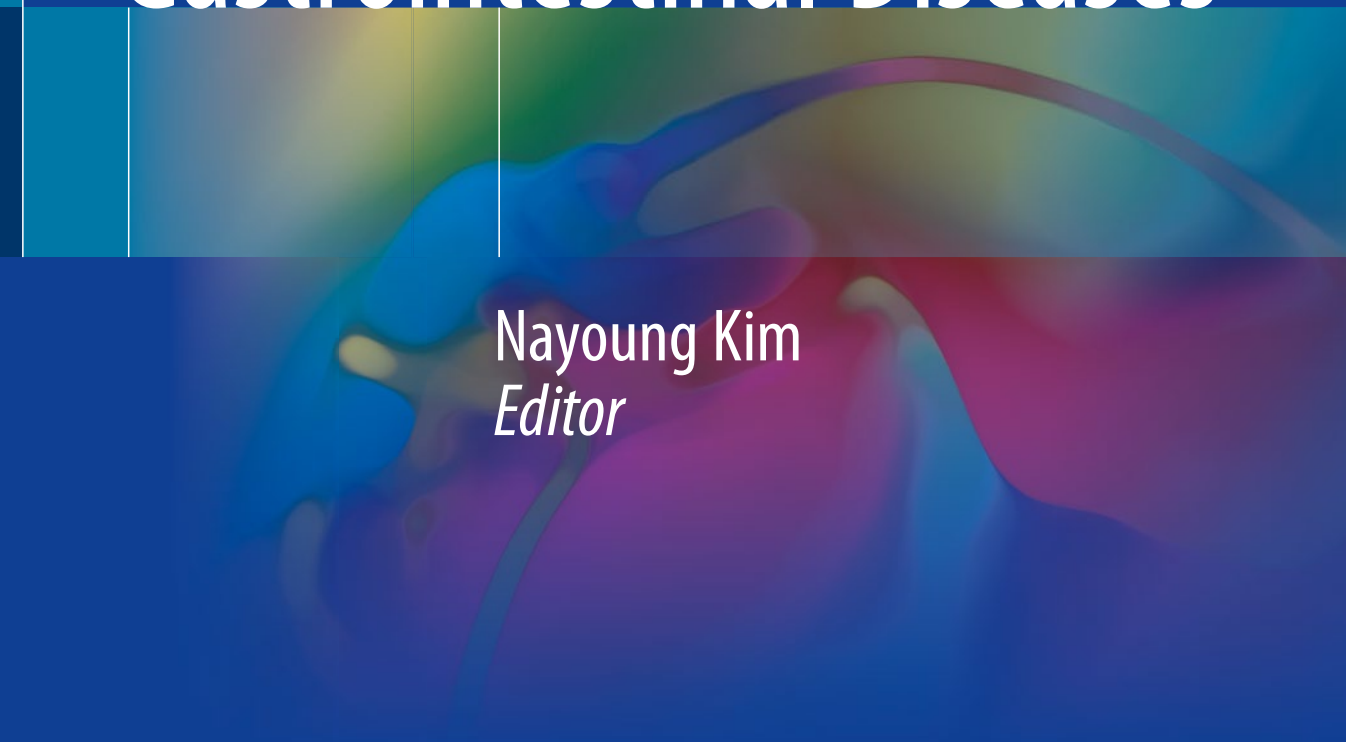
Sex/Gender-Specific Medicine in the Gastrointestinal Diseases



Nayoung Kim
Editor

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Preface

Now it is the 4th pandemic era of COVID 19. Over 50% of the world population are vaccinated while there is some variation depending on each country. However, I wonder whether the effect of COVID vaccination is equally effective for a man with 185 cm height/110 kg weight and a woman with 145 cm/40 kg. Maybe it will be different in terms of pharmacokinetics and pharmacodynamics which are affected by sex. In addition, the side effects seem to be different depending on sex/gender. While physicians tend to agree that children are not miniature adults, few recognize that women are not simply smaller men. For many, women and men were considered the same except for reproductive organs. In the 1980s and 1990s, the realization that medicine as a whole—including the diagnosis and treatment of diseases—is male-centered led to a focus on women's health such as endocrine and reproductive systems. With new studies of sex/gender differences in diabetes and cardiovascular diseases, sex became recognized as an important biological variable. Although many researchers and clinicians believe that sex differences are already well understood, experts point out that even where females and males are included in a study in equal numbers, data are frequently not analyzed according to sex. As a result, medical studies tend to present an "average" for each disease—an average that may not accurately describe either females or males. This issue is very important because studies that fail to disaggregate and analyze data by sex miss specific disease mechanisms and treatments for women, men, and non-binary people. For example, estrogen receptors (ERs) have widespread effects in numerous cells throughout the body, not just in reproductive organs. This means that differences between females and males in estrogen levels impact cells well beyond the reproductive system. In light of these findings, researchers have been actively investigating conditions where the disease incidence is higher in one sex, or where clinical manifestation is different between women and men even in cases where the disease incidence is similar.

While I have been a gastroenterologist for 30 years, I first encountered the concept of "Gendered Innovation" or "Sex/Gender-Specific Medicine" in 2014 when I joined the GI Workshop cosponsored by Stanford University, National Science Foundation, Korea Foundation of Women's Science & Technology Associations (KOFWST). The workshop was held at Stanford University and colorectal cancer (CRC) was one of the topics in this workshop. In particular, the sex/gender-specific aspect of colon cancer was very

impressive and attractive as a research topic. The incidences of gastrointestinal (GI) cancers such as esophageal, gastric, colorectal, and hepatocellular carcinoma are higher in men compared to women, suggesting the protective role of estrogen in the GI cancers. Sex difference of GI cancers has two aspects between sexual dimorphism (biological differences in hormones and genes) and gender differences (non-biological differences in societal attitudes and behavior). It is opposite in the case of functional gastrointestinal disorders (FGID). FGIDs, such as functional dyspepsia and irritable bowel syndrome, are more common in women than in men and are related to sociocultural factors such as stress, which tend to differ by gender. Various mechanisms of FGID have been proposed, such as disturbed gastroduodenal motility and visceral hypersensitivity. Women with FGID more commonly have visceral hypersensitivity and are more strongly influenced by the brain-gut axis. Physiological mediators such as ghrelin and transient receptor potential vanilloid-1 (TRPV1) play a significant role in the pathophysiological mechanism of functional dyspepsia in men, but factors related to the brain-gut axis, such as depression and anxiety, play a larger role in women. Women and men frequently are presented with different symptoms of FGID and respond differently to treatment. These differences can be caused by the effects of sex hormones or genetic predispositions on disease mechanisms (i.e., pathophysiology) and by sociocultural factors related to gender. This book highlights the sex/gender differences in the diseases of entire GI organ. Especially regarding the gut and oral microbiota, which affect various parts of a person's body from brain to gut, neurologists, psychiatrists, and dentists as well as gastroenterologists collaborated to uncover the sex/gender difference of depression, anxiety, cognitive disorders and Parkinson's disease. These chapters clearly show that studies must integrate both sex and gender analysis into the research design and analyze how sex and gender interact with each other.

I would like to thank the co-authors of this book, Prof. Hee Young Paik and Prof. Heisook Lee for their encouragement on publishing this book, and Prof. Londa Schiebinger for her help with kind and accurate comments regarding the "Why Is Sex/Gender-Specific Medicine Needed?" The quality of this book was upgraded by Ji Hyun Park who played the role of manuscript editor very well. Finally, I hope this book stimulates the interests of researchers and clinicians worldwide in terms of "Sex/Gender-Specific Medicine."

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Introduction

Sex/gender-specific medicine (SGM) is defined as the practice of medicine based on the understanding that biology and social roles are important in men and women for prevention, screening, diagnosis, and treatment. Current research demonstrates differences in disease incidence, symptomatology, morbidity, and mortality based on sex and gender. Sex/gender-specific medicine is a fundamental aspect of tailored therapy and precision medicine. Therefore, the variables must be considered in medical education and practice as well as in research models ranging from human participants, animals, and cells. Gastroenterology is very big and important division of Internal Medicine, which include esophagus, stomach, small and large intestine, pancreatobiliary tract, and liver. Nowadays, estrogen is known to play a key role in the prevention of colon cancer and progression of liver cirrhosis and hepatocellular carcinoma, especially in women. In this book, I tried to cover the sex/gender-specific medicine in the area of GI tract in the adults as well as in the pediatrics and in the gut microbiota.

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Part I

Why Is Sex/Gender-Specific Medicine Needed?

Why Is Sex/Gender-Specific Medicine Needed?

1

Nayoung Kim and Londa Schiebinger

1.1 Introduction

Medical researchers and clinicians recognize that it is important to understand differences related to age, for example, between young and old people. Similarly, it is important to understand the physiological/physical differences among women, men, and non-binary people. The differences among women, men, and non-binary people can be divided into sex differences, which respond to hormones and genetic factors, and gender differences, which are related to differences in women's and men's distinct social and cultural roles. Importantly, these two aspects—sex and gender—interact and together influence health outcomes [1, 2]. Thus sex and gender are modifiers of health, disease, and medicine [3]. For instance, emerging research reveals that lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) individuals experience higher rates of health disparities [4–6]. These disparities may be driven, in part, by medical providers' biases and lack of knowledge in health-care settings [4–7]. There has been a tectonic shift in the field of transgender health care since the 2007 [8], but little is known about how medical, nursing, or dental students are trained to identify and reduce the effects of their own biases toward LGBTQ+ individuals. New strategies are needed to assess and mitigate implicit bias toward LGBTQ+ patients [7].

Sex/gender-specific medicine refers to the health-related differences between women and men. Although many researchers and clinicians believe that sex differences are already well understood, experts point out that even where females and males are included in a study in equal numbers, data are often not disaggregated and analyzed by sex. As a result, medical studies tend to present an "average" for each disease—an average that may not accurately describe either females or males. This issue is very important because studies that fail to disaggregate and analyze data by sex miss specific disease mechanisms and treatments for women, men, and non-binary people [9]. For example, estrogen receptors (ERs) have widespread effects in numerous cells throughout the body, not just in reproductive organs. This means that differences between females and males in estrogen levels impact cells well beyond the reproductive system. In light of these findings, researchers have

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been actively investigating conditions where the disease incidence is higher in one sex or where clinical manifestation are different between women and men even where the disease incidence is similar. Prominent examples include brain development, cardiovascular disease in women, osteoporosis in men, and stem cell research [10].

It is important to understand that sex/gender-specific medicine is part of the move toward precision medicine. This review presents the history of sex/gender-specific medicine along with a discussion of the definition, development, and importance of sex/gender-specific medicine in gastrointestinal (GI) diseases.

1.2 History of Sex/Gender-Specific Medicine

Physicians tend to agree that children are not miniature adults. However, few recognize that women are not simply smaller men. For many, women and men were considered the same except for reproductive organs. In the 1980s and 1990s, the realization that medicine as a whole—including the diagnosis and treatment of diseases—is male-centered led to a focus on women's health [11]. Initial interest focused on the endocrine and reproductive systems, but with new studies of sex/gender differences in diabetes and cardiovascular diseases, sex became recognized as an important biological variable. Further studies emphasized the role gender plays as a sociocultural variable in disease [12] (Fig. 1.1), and the term "gender medicine" was coined [13]. In the 2000s, the term "sex/gender-specific medicine" was established as a concept that includes the interaction of both biological and sociocultural aspects in health outcomes.

1.3 What Is Sex/Gender-Specific Medicine?

Sex/gender-specific medicine refers to the study of medicine that integrates both biological and sociocultural roles of females and males into the

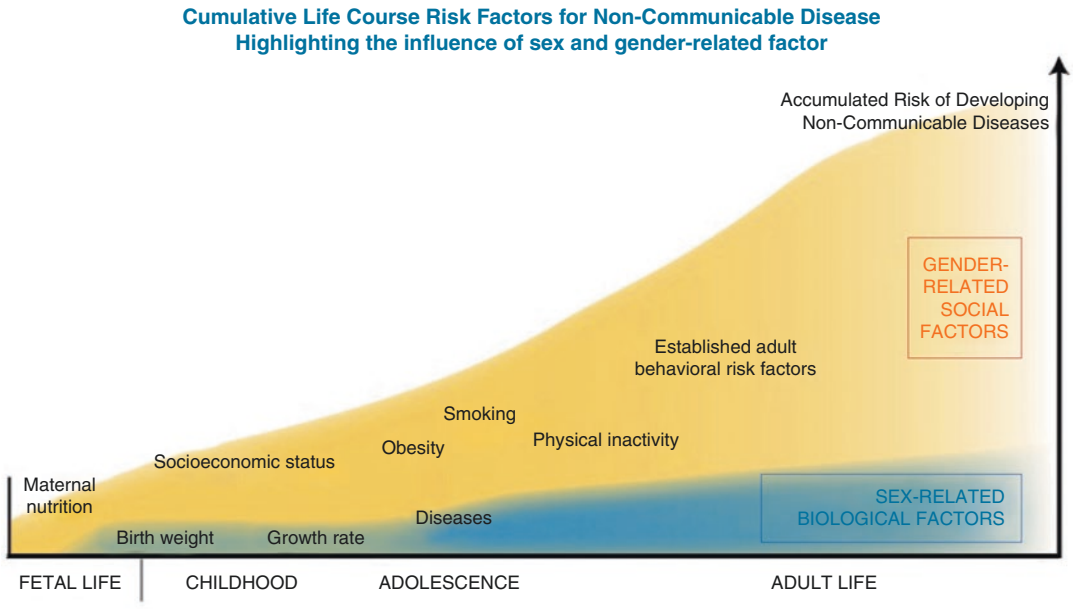

Fig. 1.1 Risk factor analysis of non-communicable diseases by life stages with a focus on sex/gender elements (adapted from Danton-Hill et al. [12])

screening, diagnosis, treatment of disease, and clinical practice. Recent studies have documented significant differences between women and men in the incidence, symptoms, morbidity, and mortality of various diseases [14], highlighting the importance of sex/gender-specific medicine to precision medicine [8, 15]. It is important to understand that sex/gender-specific medicine is not women's health, which focuses primarily on women's reproductive health. Rather sex/gender-specific medicine analyzes differences between men and women throughout the entire body and recognizes that understanding these differences will improve the precision and quality of health care for both women and men.

The next step is to integrate sex/gender-specific medicine into the medical curriculum. In recent years, Western societies, such as the United States, Germany, and Sweden, have incorporated sex/gender-specific medicine into clinical training programs for medical students, graduate students, and medical personnel [16]. There have been release of three online training modules for integrating sex and gender in biomedical research; primary data collection with humans; and the analysis of data from human participants from the Canadian Institutes of Health Research (CIHR). In addition, release of sex as a biologic variable (SABV) primer consists of four interactive courses with title of SABV and health of women and men, SABV and experimental design, SABV and analysis, and SABV and research reporting from US National Institutes of Health. These courses have been evaluated positively [17]. From these experiences, the experts found that sex/gender-specific findings must be incorporated across the curriculum—wherever relevant—at all levels education for medical students, graduate students, residents, and fellows [18–20]. To achieve this goal, more educational materials, case studies, and clinical reports and studies are needed [16, 18].

From 2017 to 2019, South Korea experimented with two courses. One was offered as an elective for second-year medical students at the Seoul National University College of Medicine and received positive reviews. A second course was offered to graduate students in translational medicine in 2017 and 2019. This course employed the text, *Sex and Gender Aspects in Clinical Medicine* [15]. This foundational text reported finding for sex and gender in circulatory, respiratory, digestive, kidney, and autoimmune diseases, as well as endocrinology, hematology, neurology, clinical pharmacology, and pharmacokinetics [15, 21]. Faculty and students who took the course were unfamiliar with sex/gender-specific medicine before attending the classes, but by the end of the semester, they were motivated to apply sex/gender-specific analysis to their clinical research [22] (Table 1.1). This experience was published as an article entitled "Experiences with a graduate course on sex/gender medicine in Korea," [22] which received considerable attention.

1.4 The Need for Sex/Gender-Specific Medicine

Why is sex/gender-specific medicine necessary? Ultimately, the reason is that sex/gender-specific medicine improves health outcomes [15]. Women and men may suffer from different diseases; they may also present with different symptoms in the same disease. Biologically, these differences may be caused by the effects of sex hormones or genetic predispositions on disease mechanism (i.e., pathophysiology). Culturally, these differences may be traced to gender differences in social roles, attitudes, and behaviors, which may impact the incidence or expression of disease. Some prominent examples of sex and/or gender differences in disease include myocardial infarction, the clinical symptoms of heart failure, rheumatic disease, and autoimmune diseases. For instance, myocardial infarction and sudden ischemic death is more common in men, meaning that treatment is often delayed in women who may present with atypical symptoms, such as epigastric soreness or heaviness instead of pain in the chest. Since coronary syndrome related to stress is more common among women, exercise stress testing is less effective for women than for men.

Table 1.1 Survey of participants in a graduate course on sex/gender-specific medicine in the graduate school of translational medicine in a Seoul-based medical school (adapted from Park et al. [22])

Items	Pre class (n = 22)	Post class (n = 20)	p-value
I am familiar with sex/gender differences in medicine			<0.0001
Strongly disagree	1 (4.5)	1 (4.5)	
Disagree	12 (54.5)	0	
Neutral	8 (36.4)	8 (36.4)	
Agree	1 (4.5)	9 (40.9)	
Strongly agree	0	2 (9.1)	
I am familiar with the term "gendered innovation"			<0.0001
Strongly disagree	6 (27.3)	1 (4.5)	
Disagree	10 (45.5)	4 (18.2)	
Neutral	6 (27.3)	7 (31.8)	
Agree	0	7 (31.8)	
Strongly agree	0	1 (4.5)	
Sex/gender-based medicine is a fundamental aspect of precision medicine or research			0.287
Strongly disagree	0	0	
Disagree	1 (4.5)	1 (4.5)	
Neutral	3 (13.6)	0	
Agree	8 (36.4)	7 (31.8)	
Strongly agree	10 (45.5)	12 (54.5)	
Sex/gender-based medicine is a fundamental aspect of precision medicine or research			0.724
Strongly disagree	0	0	
Disagree	1 (4.5)	1 (4.5)	
Neutral	5 (22.7)	0	
Agree	11 (50.0)	9 (40.9)	
Strongly agree	5 (22.7)	10 (45.5)	

Differences are common in other diseases. The ratio of women to men among patients with rheumatoid arthritis is 2 to 3:1. Although there are no specific clinical differences, women tend to evaluate their pain as more severe than do men, meaning that disease activity is greater in women. In addition, women suffer comorbidities, such as depression, thyroid disorders, and fibromyalgia, while men suffer more cardiovascular diseases. Experts in these fields may be familiar with these differences but students, interns, and residents rarely are. Another example is sex/gender difference in prediabetes. Glucose intolerance occurs quickly in women, but in men, fasting blood sugar rises only gradually in these early stages. The cardiovascular comorbidities of diabetes are also different for women and men. Thorough familiarity with these differences can assist in diagnosis and treatment, underscoring the need for sex/gender-specific medicine [15].

1.5 Need for Sex/Gender-Specific Medicine in Gastrointestinal Diseases

Functional gastrointestinal disorders (FGIDs), such as gastroesophageal reflux disease, functional dyspepsia (FD), and irritable bowel syndrome (IBS), are more common among women. Stress is an important factor in these diseases, and women are more susceptible to stress; therefore, considering gender differences in treatment is important. Visceral hypersensitivity and mobility, important elements in the mechanism of these diseases, are regulated by the brain-gut axis, which is also influenced by gender. It is often difficult, however, to define gender and analyze it in research. GI cancers (e.g., esophageal cancer, gastric cancer, and colon cancer) are known to be twice as prevalent in men as in women, but it is not clear whether there are reasons for this

beyond gender-specific discrepancies in smoking, which is more common among men, and differences in alcohol and food consumption. Finally, liver fibrosis that progresses after hepatitis B or C infection is common in men, but rare in women.

Estrogen plays a role in these and other diseases. Interestingly, disease patterns and incidence in men and women differ more before menopause and become more similar after menopause. Estrogen is a steroid hormone first discovered as a substance that controls the development and growth of human reproductive organs. Estrogen and estrogen receptors, however, have been shown to be involved in physiological and pathological processes extending well beyond the reproductive organs to the cardiovascular, skeletal, and neuroendocrine systems [23]. Research on estrogen entered a new phase when two different types of receptors (ERα and ERβ) were discovered in 1996, which has prompted wider-ranging research. Similarly, androgen receptors (ARs) are a new target of research. ARs have been found to be involved in cancer mechanisms in tissues other than reproductive organs. AR overexpression promotes carcinogenesis and is related to lymph node metastasis and poor prognoses [24, 25]. A study of neoplastic tissue of the stomach showed that AR positivity was independently associated with lower survival rates; connections to other clinical and pathological factors were not found [26, 27].

Colon cancer also displays both sex/gender differences. Color cancer is more prevalent among men. The low incidence of colon cancer in women may relate to ERβ which inhibits colon cancer [28, 29], especially since, after menopause, the incidence in women rises. Gastric cancer is also more common in men than in women, with a 2:1 ratio [30]—a pattern that is consistent across the world. Its incidence, however, may be age dependent since gastric cancer in men differs across age groups [31, 32]. Approaches from various perspectives are necessary to understand the factors that might explain a higher prevalence of gastric cancer in men. Environmental factors related to tumors should be comprehensively analyzed along with genetic factors related to the X and Y chromosomes, differences in sex hormones, lifestyle factors including smoking and drinking, *Helicobacter pylori* (*H. pylori*) infection [33], and the gut microbiome. Among the known risk factors of gastric cancer are *H. pylori* infection, alcohol consumption, and smoking. These all contribute to a higher incidence in men, but these factors do not fully explain the difference.

Rates of AR positivity in gastric cancers are not significantly different for women and for men [34, 35], but studies have reported that the occurrence of undifferentiated adenocarcinoma are significantly more frequent than that of differentiated adenocarcinoma in AR-positive patients [35]. More recent studies have demonstrated associations between AR status and cancer stage in gastric cancer [36, 37]. One study also reported that AR expression was related to diffuse gastric cancer and a lower disease-free survival rate [38]. However, these studies fail to fully explain sex/gender differences in gastric cancer. In many clinical studies, sex was not considered as a biological variable; therefore, data regarding various factors related to sex hormone exposure were not even collected. Thus, analyses using big data or prospective data are essential to demonstrate the theoretically likely evidence of sex/gender differences in gastric cancer. In vitro studies remain inconclusive because the sex of experimental cells, tissues, or animals is often not registered. For instance, Taylor et al. [39] reviewed articles published in 2010 to determine the extent to which the sex of cells was reported in cardiovascular studies. They found that, among 191 articles published in top cardiovascular journals, only 45 articles (23.6%) reported cell sex [39]. Among these studies, most (68.9%) used only male cells, and none exclusively used female cells [39]. This situation is not limited to any one research field. Shah et al. [40] reported that only 25% of 100 articles randomly selected from the *American Journal of Physiology-Cell Physiology* published in 2013 described the sex of cells used in

experiments [40]. An analysis of major cell banks—e.g., American Type Culture Collection, European Collection of Cell Cultures, and Japanese Collection of Research Bioresources—revealed that, of the human cell lines supplied worldwide in 2013, 20% lacked any sex description. This failure to identify sex was worse among non-human cell lines, with 92% of mouse and 83% of rat cell lines being sold without sex identification [41].

Many approaches to cancer research will materialize in the coming years. From the perspective of homeostasis of cancer stroma and organs, the regulation of angiogenesis or inflammation by sex hormones is expected to be an important foundation for understanding sex/gender differences in cancer progression. As anticancer therapy based on immune checkpoint inhibitors increases, understanding how the immune system differs by sex/gender will become an essential area of research. Based on successes reported for lung cancer and melanoma, clinicians may extend the survival period of gastric cancer patients using programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitor agents. Much research is now focused on target groups that can benefit from these drugs. However, studies have failed to investigate potential interactions between the immune response to cancer and sex hormones. Estrogen and androgen may impact the mechanism, treatment, and prognosis of GI cancers, but research in this area is scarce, underscoring the need for sex/gender-specific analysis in GI diseases. In spite of the promise of nanomedicine to transform conventional medicine, significant numbers of therapeutic nanomedicine products have failed in clinical trials mainly because most studies have overlooked several important factors, including the significance of sex differences at various physiological levels [42]. Hajipour et al. suggested that more thorough consideration of sex physiology, among other critical variations (e.g., health status of individuals), may enable researchers to design and develop safer and more efficient sex-specific diagnostic and therapeutic nanomedicine products [42].

1.6 Conclusions

Health differences between women and men can be divided into sex differences, grounded in hormones and genetics, and gender differences, related to social and cultural roles. These two aspects are interconnected and impact the incidence of various diseases. Sex/gender-specific medicine refers to the medical study of these differences between women and men. On the side of sex, estrogen and estrogen receptors ERα and ERβ are involved in physiological and pathological processes in the cardiovascular, skeletal, and neuroendocrine systems—beyond the reproductive system [24, 25]. Similarly, ARs influence various pathways related to carcinogenesis in tissues other than reproductive organs. On the side of gender, numerous functional GI disorders, such as FD and IBS, are exacerbated by stress. It is therefore imperative that researchers better understand the mechanisms by which sex interacts with gender, especially in non-communicable diseases. To ensure the health of all of women, men, and non-binary people, it will be important to strengthen research into the sex/gender-specific aspects of GI diseases.

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Part II

Sex/Gender Differences in the Gastrointestinal Diseases

2 Sex/Gender Differences in the Gastrointestinal Diseases

Nayoung Kim

2.1 Introduction

Men and women are alike in many ways, but the biological and behavioral differences between the two sexes/genders are of considerable importance. These differences impact the prevalence, epidemiology, and pathophysiology of major diseases, as well as access to healthcare. Despite knowledge about these important differences, it is not common for clinicians to provide tailored medicine based on gender or to consider risk factors based on gender in the prevention, management, and examination of diseases. Overlooking these important factors interferes with effective treatment, and standardizing all aspects of medical practice to focus on 170-cm-tall men weighing 65 kg constitutes a major obstacle to the development of public health. To rectify this problem, wide-ranging initiatives are necessary, among which the most important is sex/gender-specific medicine, which researches differences between women and men from a medical standpoint and applies the concept of gender in clinical practice and pharmaceutical development. Sex refers to biological differences, such as reproductive functions, sex hormone levels, genetic differences expressed by the X and Y sex chromosomes and their effects, and higher body fat composition in females. In contrast, gender is related to behavior, lifestyle, and experiences [1]. Gender shapes healthcare access, healthcare usage, and behavioral attitudes toward medical professionals. Some examples of gender differences include the use of preventive methods, prescriptions of medicines, health insurance reimbursements, and receptive attitudes toward artificial pacemakers or heart transplant surgery. Sex/gender are closely related, which makes it difficult to differentiate the effects of sex/gender in reality. On the one hand, sex influences behavior, as exemplified by the fact that testosterone causes more aggressive behavior and leads to a neglect of personal safety when exposed to danger. On the other hand, gender-based behaviors can also change biological factors. For example, stress, environmental toxicity, and poor nutrition and lifestyle cause genetic or epigenetic changes in adults, children, and even fetuses [1]. Sex hormones influence gene repair and epigenetic mechanisms; therefore, epigenetic variations and their physiological effects are also different in men and women [1] (Fig. 2.1). For this reason, the effects of sex/gender should be considered in medicine. Sex/gender-specific medicine or gender medicine refers to an approach to medicine that considers the effects of biological and sociocultural factors on women and men. This chapter examines functional gastrointestinal disorders

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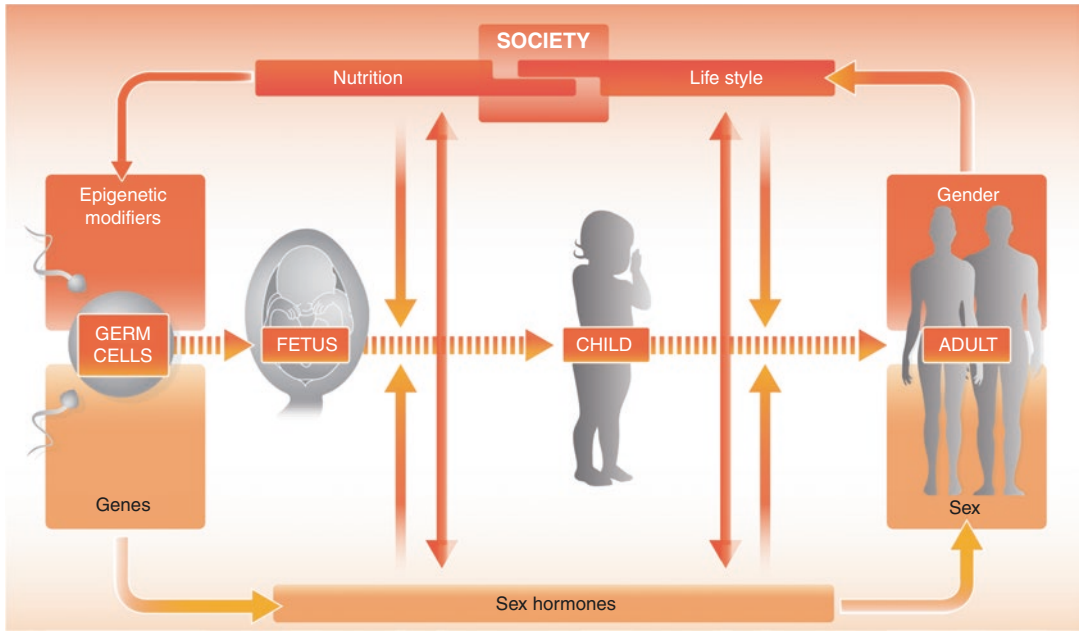

Fig. 2.1 Role of sex hormones. Since sex hormones influence gene repair and epigenetic mechanisms, epigenetic changes and their physiological effects also appear differently in men and women (adapted from Regitz-Zagrosek [1])

(FGIDs) and alcohol-related gastrointestinal (GI) diseases, for which the distinction between sex/gender is clear, and presents considerations necessary for effective treatment from the public health perspective.

2.2 Effects of Sex/Gender on Disease

Sex, which is determined by biological characteristics, is generally categorized into female and male. This categorization is based on the composition of the chromosomes that influence the expression of phenotypic features, the reproductive organs, secretion of certain hormones, and the biological functions caused by environmental factors [2–4]. In contrast, gender is determined by socially and culturally shaped attitudes and behaviors and is generally categorized into feminine/femininity and masculine/masculinity [2–4]. Some females can have a more masculine gender identity, and some males can have a more feminine gender identity. Aspects of gender identity and presentation can change even in one person throughout the stages of life due to changes in the environment or the effects of hormones. In recent years, diversity has been embraced, and the absolute influence of parents has become relatively weaker, making this tendency more evident. In the past, based on the idea that males should be masculine and females should be feminine, parents reinforced behaviors that fit this idea and discouraged behaviors that did not. However, in the modern era, when extended families have been replaced by nuclear families, the phenomenon of discrepancies between sex/gender has become more common as the influence of parents has grown weaker. Gender-related terminology varies across countries and cultures; although the system used in one country [5] may not be applicable to others, women are generally referred to as females and men as males in articles. Sex is a fundamental factor in all life sciences research, including medical research, and plays an important role in the determination of research priorities, the establishment of hypotheses, and research design [1].

In contrast, gender analysis is applied in research on topics for which sociocultural aspects

play an important role, and it is an important framework for diseases such as FGIDs in which sociocultural aspects have a large impact. However, inconsistencies in the definition of gender have led to difficulties, such as the interchangeable use of the terms sex/gender in the same paper or the use of different definitions by different authors. Biological and social factors related to sex/gender interact to influence the risk of noncommunicable diseases until adolescence, but as individuals enter adulthood and approach old age, the importance of gender, which is related to social factors, becomes greater than that of the biological factor of sex [6].

2.3 Effects of Sex/Gender on FGIDs

The gender-related (i.e., social) factors related to FGIDs can be summarized as follows [7]. First, psychological stress is associated with the symptoms and severity of FGIDs such as IBS [8]. Second, a history of sexual, physical, and emotional abuse is more common in women with IBS [9–13]. Third, women feel more embarrassment related to losing control of their bodily functions than men [4] because women consider their body functions to be private and tend to think that body functions should be kept a secret, according to how they were educated [14]. For example, men tend to experience abdominal bloating as simply a form of physical discomfort. However, for women, due to the social perception that women should be pretty and thin, abdominal bloating also becomes a cause of psychological stress because it appears that they have a protruding abdomen [15]. Beyond prejudices around appearance, women usually have to take on caregiving roles in social relationships and are raised with the norm of pleasing others by sacrificing themselves [4]. Unlike men, women are perceived to be hysterical when they express anger, make demands, or question authority. Women's opinions are ignored, and their femininity is questioned. Due to these social expectations, women might suppress certain thoughts, emotions, and behaviors rather than express them and jeopardize their relationships. For example, research has found that women with IBS had a higher self-silencing score than women with inflammatory bowel disease [16]. In contrast, men were found to struggle with losing control at work due to the symptoms of IBS [15]. Fourth, many studies have reported gender differences in the health-related quality of life of patients with FGIDs [17, 18]. In a European study, the quality of life was lower in women with IBS than in men with IBS [19]. A similar finding was also reported in a Chinese study [20]. A study that compared the quality of life of patients with FGIDs to that of healthy individuals reported that the quality of life among FGID patients was lower than that among healthy individuals, while the quality of life of women with FGID was significantly lower than that of men with FGID [18, 21].

2.4 Effects of Sex/Gender on Alcohol-Related Gastrointestinal Diseases

Alcohol consumption is an important health risk factor in South Korea. A large proportion of the South Korean population has a lower ability to metabolize alcohol than Caucasians, which makes South Koreans more vulnerable to alcohol. Specifically, in 30% of the population, the capacity to secrete the enzyme that breaks down acetaldehyde is less than half that of Caucasians. Some individuals have only about a tenth of the capacity to metabolize alcohol, to the point they cannot break down even a single drink of alcohol. Even in individuals who have a higher capability to metabolize alcohol, toxicity occurs when an amount greater than half a bottle of *soju* (traditional Korean alcohol) is consumed due to a delay in breaking down alcohol. Females are known to be more vulnerable to alcohol than males. Diseases related to drinking alcohol include GI diseases, such as liver and pancreatic disease, as well as head and neck cancers, depression, and dementia. Alcohol-related diseases manifest differently according to sex/gender; therefore, to treat these diseases well, it is important to understand how they are influenced by sex/gender.

2.4.1 Difference of Alcohol Metabolism by Sex

Once ethanol, the psychoactive component of alcoholic drinks, is absorbed into the body, it is converted to acetaldehyde by alcohol dehydrogenase in the first stage and to acetate (the conjugate base of acetic acid, also known as vinegar) by aldehyde dehydrogenase 2 (ALDH2) in the second stage. While nearly all Caucasians and Southeast Asians carry the active *ALDH2* *1/*1 genotype, the inactive *ALDH2* *2 allele is frequently observed in East Asian populations, which have 30% *ALDH2* *1/*2 heterozygosity and 5–10% *ALDH2* *2/*2 homozygosity [22, 23]. It is known that there are considerable differences in alcohol metabolism according to the *ALDH2* genotype [24]. For individuals who cannot break down alcohol such as *ALDH2* *2/*2 homozygosity, even one shot of soju can make their face and body turn red, break out with hives, and feel itchy. In severe cases, death can be caused by respiratory failure or heart problems, so caution is needed. If a low amount of ALDH2 is secreted or the level of enzyme activity is low such as in people with the *ALDH2* *1/*2 genotype, acetaldehyde, a toxic intermediate decomposition product, accumulates in the body and causes physical symptoms such as redness of the face, headaches, and palpitations [25] (Fig. 2.2). Individuals whose face turns red after drinking a small amount of alcohol secrete lower levels of ALDH2 or have less active ALDH2 as a result of genetic factors, and their blood acetaldehyde level increases dramatically even after consuming a little bit of alcohol.

There are sex differences in alcohol metabolism. In general, 20–25% of the consumed alcohol is absorbed in the stomach, while 75–80% is absorbed in the small intestines to be detoxified in the liver [26] (Fig. 2.3a). Females weigh less than males, have a higher proportion of body fat

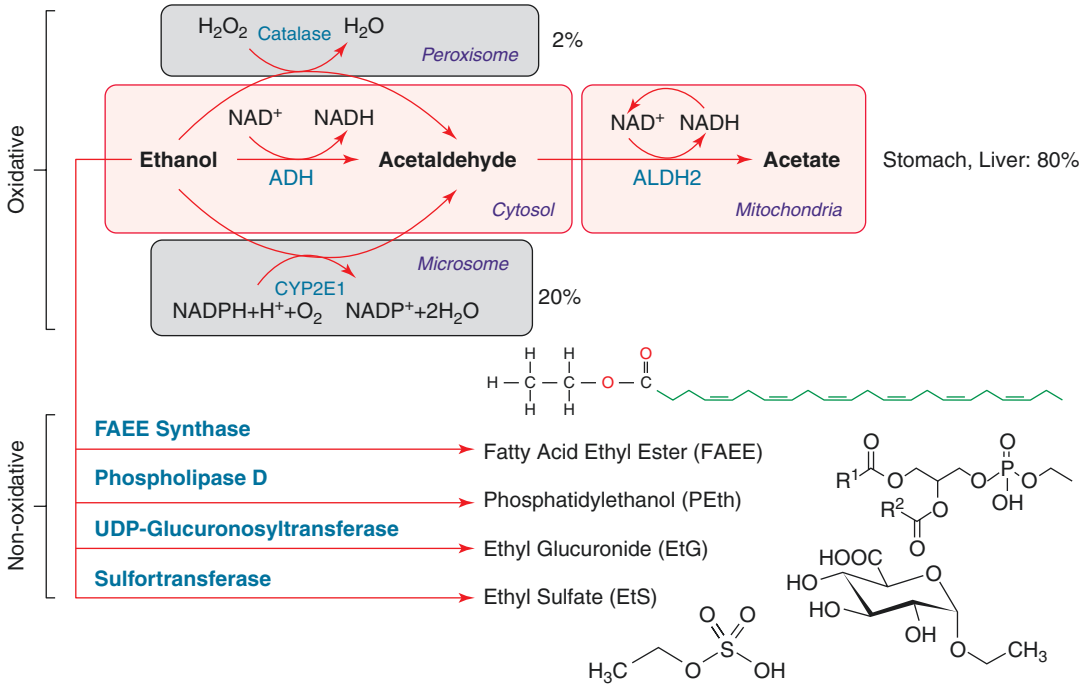

Fig. 2.2 The mechanism of alcohol metabolism. When an inadequate amount of aldehyde dehydrogenase 2 (ALDH2) enzyme is secreted or its activity is low, acetaldehyde (an intermediate product of alcohol decomposition) accumulates and causes toxicity. *ADH* alcohol dehydrogenase, *CYP2E1* cytochrome P450 2E1 (adapted from Lee [25])

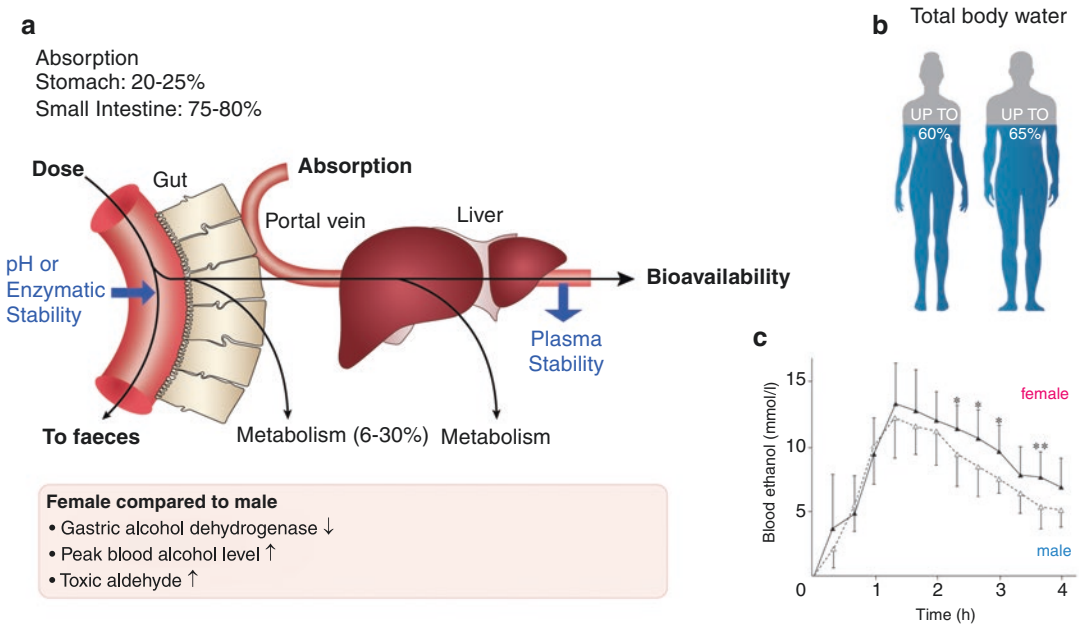

Fig. 2.3 Alcohol metabolism in men and women. In general, 20–25% of the consumed alcohol is absorbed in the stomach, while 75–80% is absorbed in the small intestines to be detoxified in the liver (**a**). Women weigh less than in men, have a higher proportion of body fat, and have a lower body water percentage (around 60% in women, 65% in men) (**b**). Since women also secrete less alcohol dehydrogenase, women have a higher blood alcohol level than men after drinking the same amount of alcohol (**c**) (adapted from van de Waterbeemd and Gifford [26])

and a lower body water percentage (around 60% in females, 65% in males) (Fig. 2.3b), and secrete less alcohol dehydrogenase enzymes; therefore, the blood alcohol level is higher in females than in males after drinking the same amount of alcohol (Fig. 2.3c), and more acetaldehyde (a toxic byproduct) accumulates in females. As a result, females have a shorter time period than males from starting drinking to the onset of conditions requiring treatment due to problems such as heavy drinking or addiction.

2.4.2 Differences in Alcohol Consumption Patterns by Gender

Throughout the world—including South Korea—alcohol consumption was traditionally considered permissible for men. In the feudal era, due to discrimination against women's consumption of alcohol, women usually drank alcohol in private spaces where they would not be seen by others. In this situation, when drinking problems occurred due to chronic alcoholism, there was generally no opportunity to make appropriate interventions. This historical trend relates to how men drink in social situations, while women drink to relieve stress. This trend is becoming clearer as women become more stressed from having to balance work and family. According to 2017 statistics, 79% of Korean men and 52.3% of Korean women consume alcohol [27] (Fig. 2.4a). When the prevalence of high-risk alcohol consumption is estimated with the World Health Organization standard of consuming more than seven drinks for men and five drinks for women once a week or consuming any amount more than twice a week, 55.8% of men and 27.6% of women have high-risk consumption [27] (Fig. 2.4b).

In recent years, alcohol consumption (both in general and high-risk consumption) has steadily become more common among women. The increase in high-risk alcohol consumption among women in their 20s and 30s has been particularly rapid (2017 Health and Welfare Statistical Year

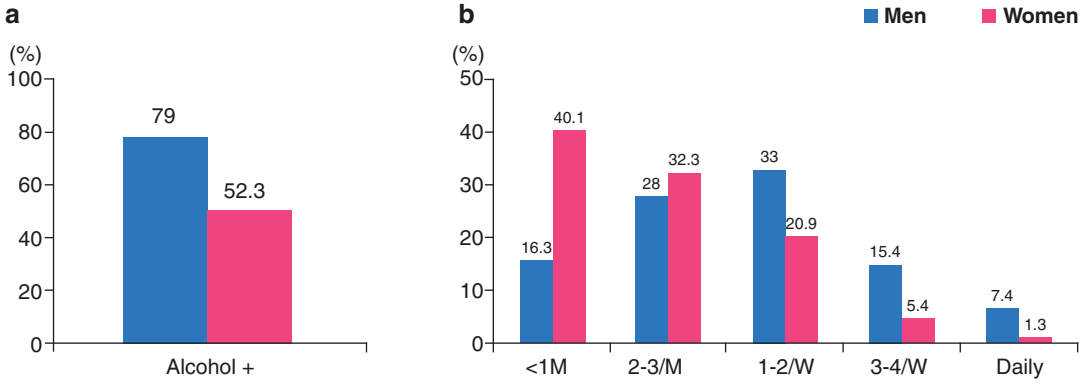

Fig. 2.4 Trends in alcohol consumption from the 2017 Health and Welfare Statistical Year Book In total, 79% of Korean men and 52.3% of Korean women consume alcohol (**a**). According to the World Health Organization standard of high-risk alcohol consumption (consuming more than seven drinks for men and five drinks for women once a week or consuming any amount more than twice a week), 55.8% of men and 27.6% of women have high-risk consumption (**b**) (adapted from 2017 Health and Welfare Statistical Year Book [27])

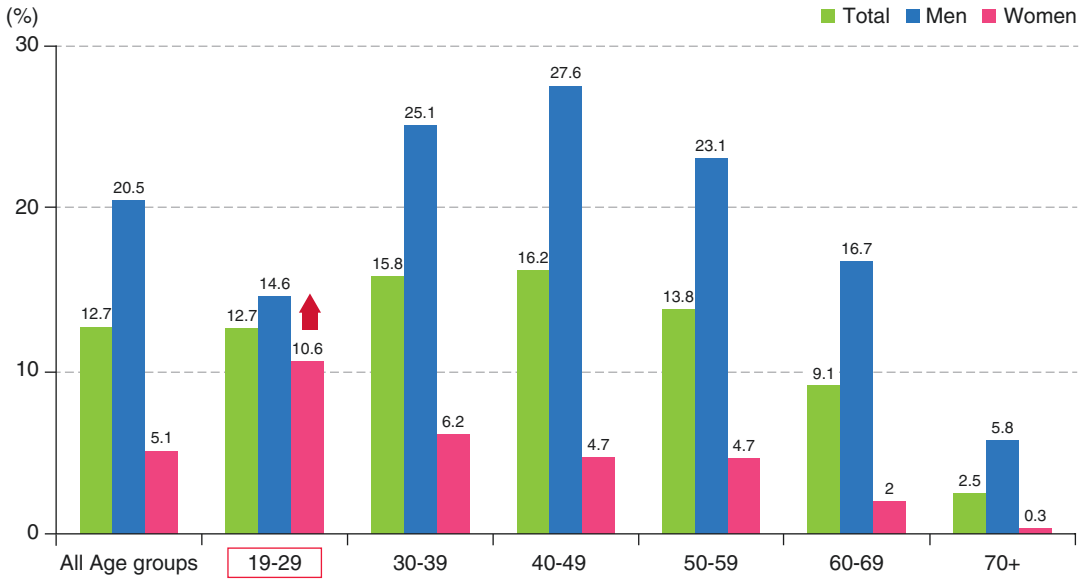

Fig. 2.5 Survey of alcohol consumption by age among South Koreans above the age of 19. Alcohol consumption is most often seen in men aged 30–59, but in women, alcohol consumption is highest among those aged 19–29 (arrow) and declines afterward (adapted from 2017 Health and Welfare Statistical Year Book [27])

Book). In a survey of the prevalence of alcohol consumption by age among South Koreans above the age of 19, drinking was found to be most common in the 30–59 age group among men, but in the 19–29 age group among women, after which the prevalence declines [27] (Fig. 2.5).

The increase in alcohol consumption among women is caused by greater exposure to drinking due to the increased participation of women aged 19–29 in the workforce, the introduction of low-proof and fruity soju targeting women, marketing efforts by the alcohol industry, and the effects of media. Delays in marriage and pregnancy are another reason. Unlike in men, alcohol consumption behavior and outcomes in women differ by occupation, income level, and education level.

Younger women with lower occupational and income status have been found to engage more frequently in high-risk alcohol consumption behaviors.

2.4.3 Differences in Healthcare Utilization by Gender Among Patients with Alcoholism

Men and women are also different in their healthcare utilization behaviors when physical diseases due to alcohol consumption occur. For several reasons, men with alcoholism are often accompanied by their spouses or other family members when visiting the emergency room or outpatient appointments. Women with alcoholism usually visit alone. As a gender difference, men tend to be more confident in front of medical staff, while women are more ashamed. Barriers to treatment exist for women, such as differences in mindset, problems with children, postpartum care, comorbid psychiatric problems, and alienation from social facilities [28, 29]. According to a report from California in the United States, when alcoholism was surveyed in a non-alcoholic clinical sample after considering gender in the general population, a greater proportion of women were found to have issues with alcohol [30]. For example, the relative risk of alcohol issues among patients in mental health treatment compared to the general population was 2.1 in men and 5.6 in women [30]. Moreover, men were more likely to have received related medical services in the past compared to women. Even when women had more severe symptoms, they were less likely to ask for help [30], which demonstrates the need for medical professionals and social workers to consider gender when they approach issues with alcohol.

2.4.4 Alcohol-Related Physical Diseases

When alcohol is not broken down due to the lack of ALDH2 secretion or reduced enzymatic activity, acetaldehyde accumulates in the body, causing various physical diseases. As described above, females are more vulnerable to alcohol and develop these diseases more quickly [31] (Fig. 2.6).

2.4.4.1 Alcohol and Esophageal Cancer

Esophageal cancer is more common in males than in females around the world, with 70% of

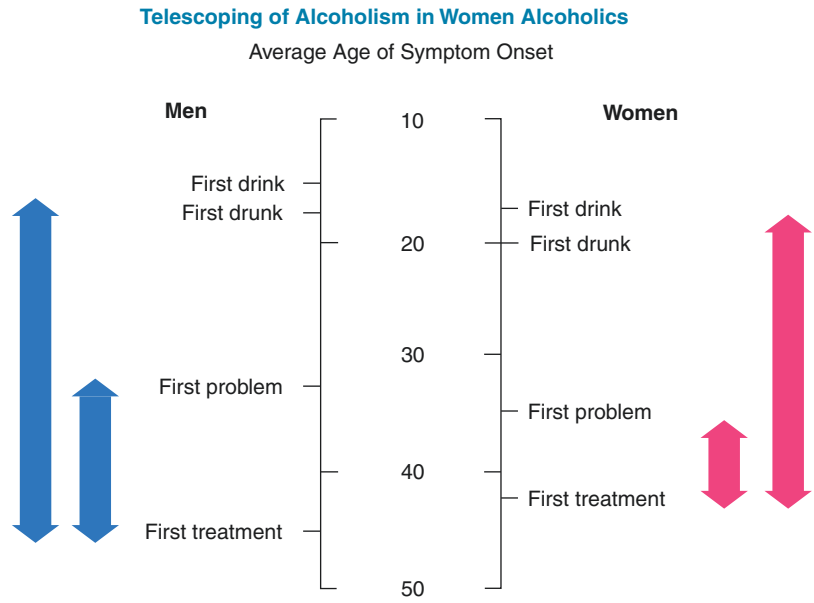

Fig. 2.6 Gender differences in the trajectories of alcoholism. The time period from the first drink to first problem and first treatment was shorter in women compared to men (adapted from Piazza et al. [31])

cases in males. In a study that analyzed data from 51,000,000 individuals in South Korea, people who consumed even a small amount of alcohol had a higher risk of GI cancer than people who did not drink at all [29]. The risk for gastric and colorectal cancer increased until the daily amount of alcohol consumption reached 20 g [29]. However, after 20 g per day, a dose-dependent increase was not observed while the risk for esophageal cancer continuously increased [29]. Among the three GI cancers, esophageal cancer was the most associated with alcohol consumption as well as with the amount of alcohol consumption [29]. In addition, consumption of both tobacco and alcohol increased the risk of esophageal cancer even further [29] (Fig. 2.7). The consumption of both alcohol and tobacco is more common among men than women. An interpretation of these findings is that due to unconfirmed causes (perhaps related to hormones), the incidence of esophageal squamous cell carcinoma or esophageal adenocarcinoma is much higher in men than women [29]. Further gender-stratified analyses of the total duration of alcohol exposure and the amount of alcohol consumed will shed further light on the effects of alcohol on esophageal cancer.

2.4.4.2 Alcohol and Gastric Cancer

Some studies reported no relationship between alcohol and gastric cancer, but the lack of an association in those studies may have been because they did not consider poor ALDH2 metabolizers. Our team investigated the association between alcohol consumption and the risk for gastric cancer in the Korean population with the *ALDH2* genotype [33]. Subjects with inactive *ALDH2* *2 allele(s) showed a lower level of alcohol consumption than *ALDH2* *1/*1 homozygotes ($p < 0.001$) [33]. Among the *ALDH2* *1/*2 carriers ($n = 243$), current/ex-drinkers had a significantly increased risk for gastric cancer compared with never/rare drinkers (odds ratio [OR] 2.80; 95% confidence interval [CI], 1.51–5.19) [33]. Among heavy drinkers ($n = 115$), *ALDH2* *1/*2 heterozygotes had a fourfold increased risk for gastric cancer compared with *1/*1 homozygotes (OR 4.26; 95% CI, 1.10–16.47); however, no risk increase was seen among never/rare drinkers. Furthermore, there was a

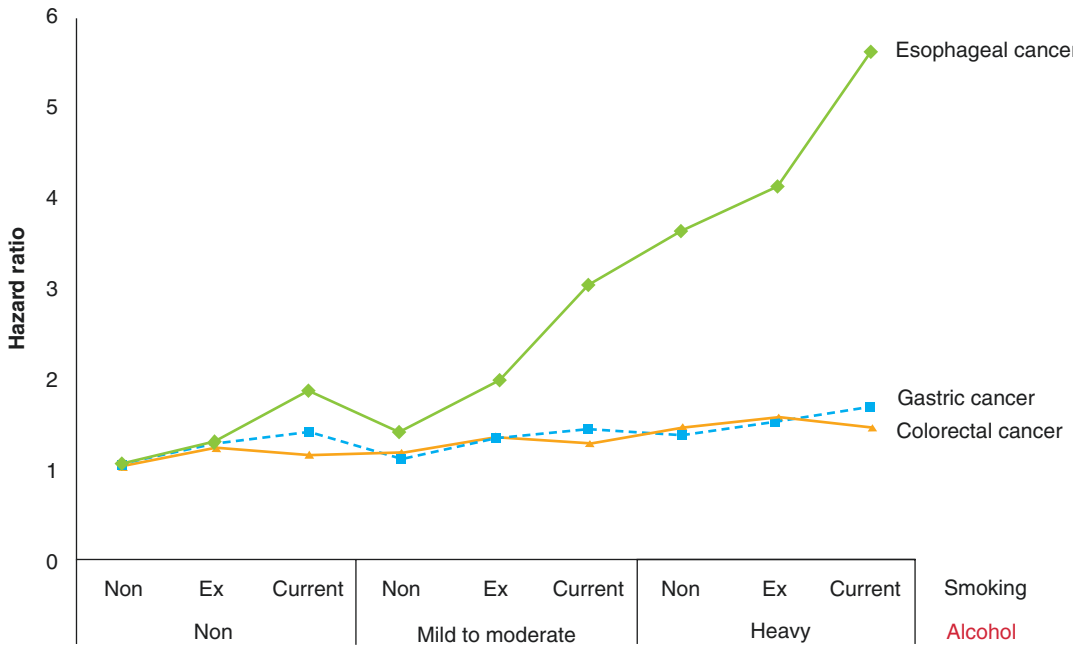

Fig. 2.7 Effects of alcohol on esophageal cancer. The combination of alcohol consumption and smoking further increased the risk of esophageal cancer (adapted from Choi et al. [32])

gender difference in the effect of alcohol. That is, no significant differences were found in males, but females showed large differences in the risk of gastric cancer, with risk increasing from non-drinkers, quitters, and light drinkers to heavy drinkers [33] (Table 2.1). Recently we performed the meta-analysis in a total of seven case–control studies on *ALDH2* rs671 polymorphism consisting of 3251 gastric cancer cases and 4943 controls [34]. Inactive *ALDH2* genotypes (G/A or A/A) were associated with an increased risk of gastric cancer (OR 1.26; 95% CI, 1.04–1.52; $p = 0.02$; $I^2 = 64\%$), compared with active *ALDH2* (G/G genotype) [34]. Subgroup analysis by alcohol consumption showed that inactive *ALDH2* increased risk for gastric cancer in moderate to heavy drinkers (OR 1.85; 95% CI, 1.52–2.25; $p < 0.01$; $I^2 = 6\%$) more than in non-drinkers or mild drinkers (OR 1.19; 95% CI, 1.05–1.36; $p < 0.01$; $I^2 = 6\%$) [34]. Moderate/heavy alcohol consumption increased gastric cancer risk in individuals with inactive *ALDH2* (OR 2.23; 95% CI, 1.63–3.05; $p < 0.01$; $I^2 = 30\%$) more than those with active *ALDH2* (OR 1.40; 95% CI, 0.98–2.01; $p = 0.07$; $I^2 = 85\%$) [34]. These results suggest that the *ALDH2* polymorphism modifies the risk of gastric cancer. However, most of studies did not analyze the effect of gender difference on the alcohol-induced gastric carcinogenesis. There was a survey about alcohol flushing could be used to measure ALDH2 activity levels [35]. Gender differences in alcohol flushing and disease need to be evaluated in the future.

2.4.4.3 Alcohol and Colorectal Cancer

In "Ten Ways to Eat and Manage Health to Beat Colorectal Cancer" published by the Korean Society of Cancer Prevention for the 2016 Cancer Prevention Day, excessive drinking was identified as a risk factor of colorectal cancer. The risk of colorectal cancer was 1.3 times [32] and 1.87 times [36] higher in heavy drinkers than in non-drinkers in studies based in South Korea, and the risk was 1.42 times higher in a Japanese cohort study [37]. In a community-based study that observed 6291 residents (aged 55 and older) of Ganghwa-do for 20.8 years from 1985 to 2005, mortality associated with soju was significantly higher than that associated with *makgeolli* (Korean traditional alcohol) among men, but this difference was not significant among women. The reason for this finding may be that the

Table 2.1 The effects of alcohol on gastric cancer by gender (adapted from Shin et al. [33])

	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)	*p* value[a]
All subjects ($n = 815$)				
Never/rare drinker	213 (47.9)	240 (64.9)	1.00 (reference)	
Ex-drinker	94 (21.1)	43 (11.6)	1.68 (1.07–2.64)	0.024
Light drinker	70 (15.7)	40 (10.8)	1.60 (0.99–2.58)	0.054
Heavy drinker	68 (15.3)	47 (12.7)	1.12 (0.70–1.81)	0.636
p_{trend}				0.335
Males ($n = 495$)				
Never/rare drinker	102 (33.2)	69 (36.7)	1.00 (reference)	
Ex-drinker	80 (26.1)	36 (19.1)	1.29 (0.77–2.17)	0.337
Light drinker	60 (19.5)	36 (19.1)	1.14 (0.67–1.93)	0.622
Heavy drinker	65 (21.2)	47 (25.0)	0.88 (0.54–1.46)	0.629
p_{trend}				0.965
Females ($n = 320$)				
Never/rare drinker	111 (80.4)	171 (94.0)	1.00 (reference)	
Ex-drinker	14 (10.1)	7 (3.8)	3.07 (1.14–8.28)	0.027
Light/heavy drinker[b]	13 (9.5)	4 (2.2)	7.24 (2.12–24.70)	0.002
p_{trend}				<0.001

[a]Logistic model adjusted for gender, age, *H. pylori* infection, smoking, and school education

[b]Light and heavy drinkers were combined among females because there were only three heavy drinkers in gastric cancer cases and no heavy drinkers in controls. Never/rare drinker refers to a non-drinker or one who drinks <2 U/week; light drinker <12 U/week; heavy drinker ≥12 U/week (1 U = 12 g of ethanol)

amount of consumption was larger and the duration of consumption was longer in men [36].

2.4.4.4 Alcohol and Chronic Liver Disease

Alcohol consumption is one of the main risk factors for liver disease and causes various liver diseases such as alcoholic fatty liver, alcoholic hepatitis, cirrhosis, and liver cancer. Alcohol can ultimately cause death by liver failure. According to the 2017 Health and Welfare Statistical Year Book, the number of patients with chronic alcoholic liver disease was declining, but the total health expenditures associated with alcoholic liver disease continued to increase. For adult men, the risk of alcoholic liver disease increased when 40–80 g of alcohol (240–480 mL of *soju*) was consumed every day, but in women, the risk increased with the daily consumption of more than 20 g of alcohol, demonstrating that women are more likely to develop alcoholic liver disease with less alcohol consumption than men [38]. Even when the same amount of alcohol is consumed, the risk of cirrhosis is higher in women than in men, and cirrhosis can occur in women who consume only one to two drinks per day [38].

2.4.4.5 Alcohol and Pancreatitis

The pancreas is an important organ that secretes insulin and digestive enzymes. Excessive drinking increases the viscosity of blood and deteriorates blood circulation. In response to increased levels of cholecystokinin, which stimulates the secretion of pancreatic fluid, digestive enzymes that break down proteins do not flow into the GI tract. Instead, these enzymes break down pancreatic tissue, causing pancreatitis. Females are at a higher risk of acute pancreatitis, wherein the pancreas swells and form blisters that narrow or block the pancreatic duct, through which pancreatic fluid flows. As alcohol consumption among women in their 20s is increasing, the incidence of pancreatitis is also increasing. Chronic pancreatitis becomes less common among men as they age, but it becomes more common among women. According to a Japanese study result, the mean age of onset of acute pancreatitis was 50 years but was lower among women than among men. There was also a small difference in the mean age of onset of chronic pancreatitis, with the mean age among women being 53.3 years, which was lower than that among men [37]. Another Japanese study examined the length of alcohol consumption until the incidence of pancreatitis by gender. The time period from exposure to excessive alcohol consumption to the diagnosis of pancreatitis was shorter in women, with 6.8 years for acute pancreatitis and 9.7 years for chronic pancreatitis. The length from first drink to the incidence of acute pancreatitis was 29.8 years for men and 22.2 years for women, and the length from first drink to the incidence of chronic pancreatitis was 34.3 years for men and 23.0 years for women [39].

2.5 Conclusions

From the perspective of the influence of sex/gender on disease, biological and social factors interact to influence disease. For noncommunicable diseases, as individuals enter adulthood and approach old age, the influence of gender, which is connected to social factors, becomes greater than that of sex, which is connected to biological factors. In other words, factors related to gender, which is shaped by the sociocultural environment, have a large impact. FGID serves as an excellent example of conditions for the role of gender is evident in patients' responses to clinical symptoms and from the perspective of quality of life. When individuals have the same symptoms of IBS, the deterioration in quality of life is more severe for women than for men due to differences in social norms and sexual identity. Other diseases on which sex/gender have an important impact are alcoholic liver disease, pancreatitis, and esophageal cancer. The metabolic process of alcohol is influenced by sex, but the consumption of alcohol and patterns of healthcare usage are influenced by gender. Due to physical characteristics such as lower levels of ALDH2 and body water percentage, females' capacity to break down alcohol is weaker than that of males. The risk of toxicity due to the accumulation of

acetaldehyde is higher in females than in males, so females are more likely to experience various alcohol-related diseases such as gastric cancer, liver cirrhosis, and acute and chronic pancreatitis. From the gender aspect, men with alcoholism more actively use healthcare and other social welfare facilities, whereas women tend to only visit the hospital with alcohol-related diseases after their symptoms deteriorate. Therefore, medical professionals should consider sex/gender when treating alcohol-related disorders.

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Part III

Metabolism of Sex Hormones

3 Metabolism of Estrogen and Testosterone and Their Role in the Context of Metabolic Diseases

Chang Ho Ahn and Sung Hee Choi

3.1 Introduction

Sex hormones define the fundamental sexual differences between men and women and form secondary sexual characteristics through puberty. They are the most important hormones in the pathogenesis of infertility, and sexual dysfunction, and also involved in glucose metabolism, muscle function, bone metabolism, and obesity. The production of sex hormones is regulated by feedback system of the hypothalamus-pituitary-gonad axis. Pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus leads to the secretion of the follicular-stimulating hormone (FSH) and luteinizing hormone (LH) in the pituitary gland. LH and FSH stimulate the production and secretion of testosterone in the testis and estrogen in the ovary. Testosterone or estrogen is, then, delivered to hypothalamus and pituitary gland for feedback control (Fig. 3.1).

However, testosterone, a leading male sex hormone, is also produced in women's ovaries and adrenal glands [1]. Although the production of testosterone in women is only 1/7–1/10 of men, women are more sensitivity to the small amounts of testosterone [2]. The role of testosterone in insulin resistance in polycystic ovarian syndrome (PCOS), which causes infertility in women, and increased fat amount in obesity, has been reported.

In this chapter, we would like to explore the metabolism of estrogen and testosterone, their role in each organ, and the difference between women and men in the clinical aspect of metabolic diseases. This basic understanding of sex hormones metabolism could broaden the knowledge for sex/gender-specific medicine.

3.2 Metabolism of Estrogen

Compounds with stereo nuclei, such as bile acid and sex hormones, are called steroid hormones. There are three types of natural estrogen produced by women: estradiol, estriol, and estrone. They are mostly produced in the ovaries but can also be produced by metabolism of adrenal androgen. The main female hormone before menopause is estradiol. After menopause, the percentage of estrone increases. Estrone is a weak estrogen, which is commonly used in postmenopausal female hormone replacement therapy. Female hormones play an important role in women's normal sexual maturation and growth of women's genital organs including vagina and uterus and also affect other organs that express estrogen receptors. Estrogen receptors are mostly

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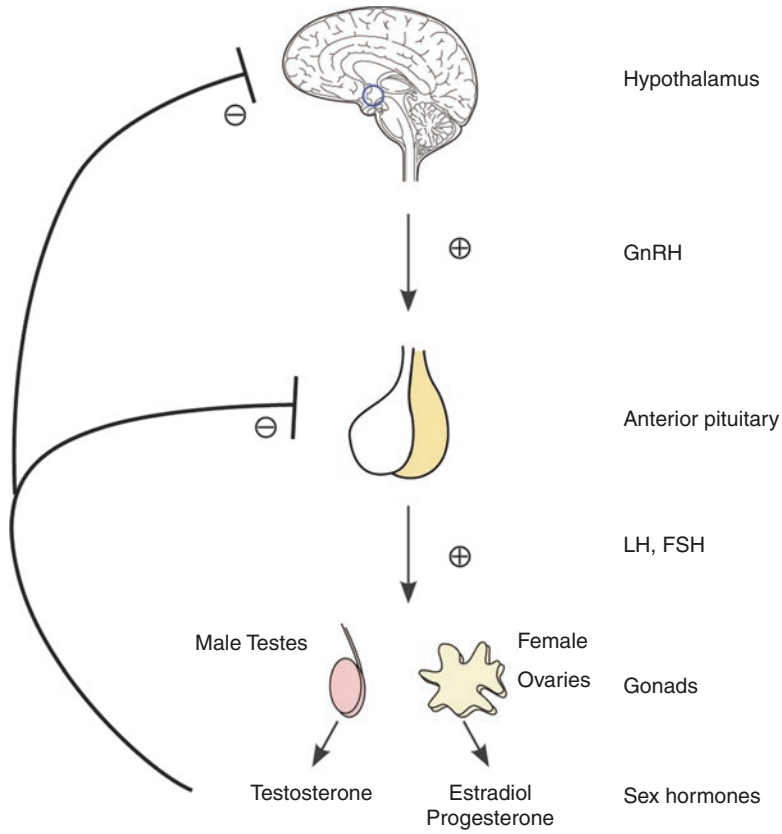

Fig. 3.1 Regulation of sex hormones. The production and secretion of sex hormones are regulated by feedback mechanism of hypothalamic-pituitary-gonadal axis (adapted from https://en.wikipedia.org/wiki/Hypothalamic%E2%80%93pituitary%E2%80%93gonadal_axis#/media/File:Hypothalamic%E2%80%93pituitary%E2%80%93gonadal_axis.svg)

nuclear receptors, but G protein-coupled estrogen receptor also exists. The main action of estrogen exerts through nuclear receptors [3–6] (Fig. 3.2).

3.3 Effects of Estrogen in the Context of Metabolic Diseases

It is well known that estrogen hormones affect bone metabolism. Estrogen contributes to the accelerated bone growth and the closure of growth plate in adolescence. In adults, the major effect of estrogen on bone metabolism is the inhibition of bone absorption. Osteoporosis, the representative of postmenopausal diseases, is 6–10 times higher in women than in men, which is related to the significant reduction of estrogen level after menopause [7, 8]. Estrogen reduces inflammatory signals such as apoptosis, oxidative stress, and NF-κB in osteoblast, while enhances apoptosis of osteoclast. Thus, without estrogen activity, bone absorption is enhanced and rapid bone loss can occur in postmenopausal women [9] (Fig. 3.3).

The effect of estrogen on bones is well demonstrated. Treatment of female hormones reduces spinal and non-spinal fractures in postmenopausal osteoporosis [10]. Estrogen has proven to reduce fractures even in women without osteoporosis. However, large cohort studies including women's health initiative (WHI) study reported

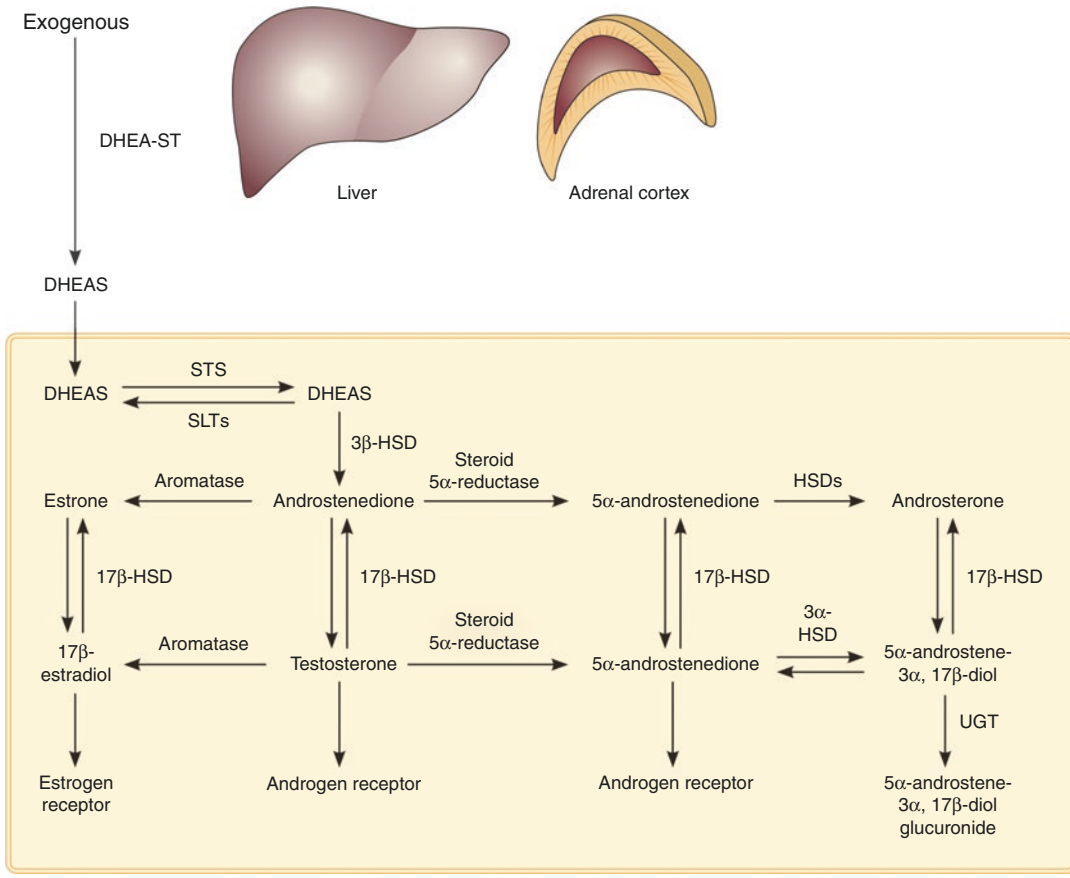

Fig. 3.2 Androgen metabolism. *DHEA* dehydroepiandrosterone, *DHEAS* dehydroepiandrosterone sulfate, *DHEA-ST* dehydroepiandrosterone sulfotransferase, *HSD* hydroxysteroid dehydrogenase, *STS* steryl-sulfatase, *SULTs* sulfotransferases, *UGT* UDP-glucuronyltransferase (adapted from Shohat-Tal et al. [6])

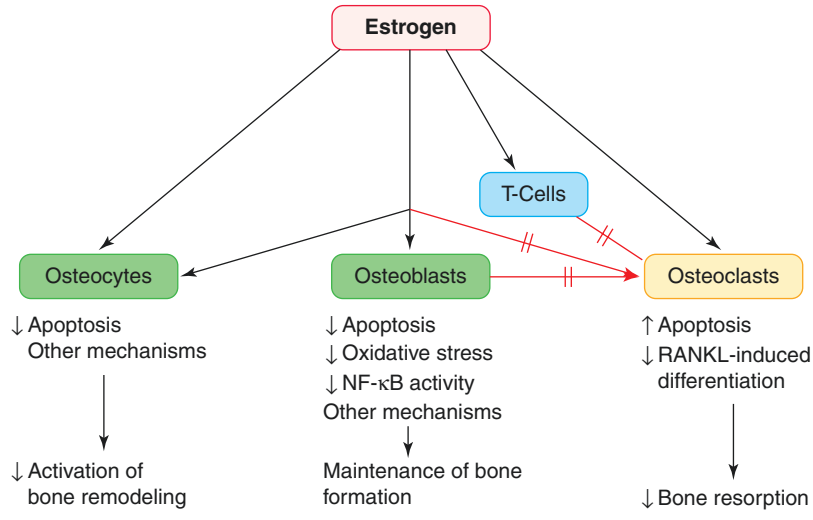

Fig. 3.3 Effects of estrogen on bone metabolism. *RANKL* receptor activator of nuclear factor-κB ligand (adapted from Okman-Klis [9])

the possibility of serious side effects such as breast cancer, endometrial cancer, cardiovascular diseases, and increased death when hormone replacement therapy was continued for a long period of time [10, 11]. As a result, female hormones are now rarely used as the primary treatment for postmenopausal osteoporosis. Selective estrogen receptor modulator (SERM) plays a dual role in inhibiting the action of female hormones in the breast or uterus and enhancing the action in the bones. Based on these characteristics, SERM is used as a treatment for osteoporosis instead of estrogen.

There is still controversy over the effects of female hormones on cardiovascular disease. The prevalence of cardiovascular disease generally increases with age, and in women, the age at which cardiovascular disease occurs is about 10 years later than in men. In particular, the prevalence of cardiovascular disease (CVD) in women increases significantly after menopause, and 95% of women's cardiovascular diseases occur after menopause. It has been suggested that the decrease of female hormones after menopause contributes to the increase of CVD [12, 13]. The effects of hormone replacement therapy in menopausal women was investigated to ensure that exposure of female hormones over a long period of time had a preventive effect on cardiovascular disease and safety of the treatment in large randomized controlled trials, but the results showed no significant reduction in cardiovascular disease after hormone replacement therapy compared to placebo [11]. Female hormones increase plasminogen, which reduces platelet adhesion, and increase high-density lipoprotein cholesterol and triglycerides. On the other hand, female hormones are known to reduce low-density lipoprotein cholesterol, the most important cholesterol for atherosclerotic cardiovascular disease [14]. In studies of blood coagulation, female hormones increase the coagulation factor II, VII, IX, and X in the liver, while reducing antithrombin III, thereby enhances blood coagulability [14]. Studies have shown that female hormone therapy in menopausal women increases deep vein thrombosis. It has been reported that the risk of thrombosis more than tripled in obese women with body mass index greater than 30 kg/m^2 [11]. Despite female hormones in premenopausal women have positive effects in lipid metabolism, maintaining vascular structure, and reducing platelet adhesion, long-term hormone replacement therapy in postmenopausal women is thought to have no significant benefits in cardiovascular disease.

Large clinical studies have reported that female hormone treatment may decrease the incidence of type 2 diabetes [15]. However, female hormone therapy has not been used to prevent T2DM by far. The WHI study also showed a 21% reduction in the incidence of T2DM in the estrogen-progesterone combined treatment group. The risk of T2DM has also decreased by 12% in estrogen-only treatment groups. These results supported the hypothesis that female hormones play a positive role in insulin secretion and sensitivity. Recent studies have also shown that estrogen regulates FOXO1 signal to promote insulin sensitivity, inhibits gluconeogenesis, and eventually contributes to blood glucose homeostasis [16]. Estrogen contributes to diabetes prevention by directly affecting the insulin resistance and secretion [17]. Previous studies showed that increased hepatic gluconeogenesis leads to impaired fasting glucose in male, while altered glucose metabolism and absorption in the intestine leads to postprandial hyperglycemia and impaired glucose tolerance in female. This may come from the differences in estrogen and androgen between the sexes [18]. Polycystic ovary syndrome, which is associated with the relative increase of androgen in female, is a well-known risk factor for T2DM. The relative increase of androgen to estrogen may adversely affect blood glucose control in women [19, 20].

Thyroid diseases are much more common in women than in men. Many studies investigated how estrogen affects thyroid function. Estrogen increases the amount of thyroid hormone binding protein, increasing the total amount of thyroid hormone. However, the amount of active hormones (free T4 and free T3) usually remains constant [21]. Recent studies have reported that

estrogen directly affects the growth of follicular cells in the thyroid. The differentiation and prognosis of thyroid cancer varies depending on the distribution of estrogen receptor subtype alpha and beta [22, 23]. Further research is expected on the role of female hormones on thyroid disease in the future.

Aforementioned differences between men and women in metabolic disease is summarized in Table 3.1 [24].

Table 3.1 Gender-specific differences of metabolic and endocrinologic diseases (adapted from Kautzky-Willer [24])

Disease	Women	Men
Diabetes	• Higher rate of impaired glucose tolerance (IGT)	• Higher rate of impaired fasting glucose (IFG)
	• Worse lipid profiles	• Increased insulin resistance and fatty liver disease
	• More pronounced endothelial dysfunction and dysfibrinolysis	• Special risk groups: men with erectile dysfunction, low testosterone
	• Higher concentrations of inflammatory markers (CRP, fibrinogen, PAI-1) and adipokines (adiponectin, leptin)	• T1DM preponderance at younger age
	• Uric acid levels and physical inactivity better predictors of T2DM	
	• Special risk groups: history of gestational DM; PCOS; high testosterone, low SHBG	
	• More comorbidities and more physical and cognitive limitations	
	• More often associated with hypothyroidism	
Obesity	• For a given BMI higher adiposity	• For a given BMI higher lean mass
	• More peripheral or subcutaneous fat mass	• More visceral and hepatic adipose tissue
	• Lower energy expenditure	• Metabolic syndrome more common
	• Higher age-adjusted increase of Metabolic syndrome (MS)	• Associated with increased lifetime risk for alcohol abuse
	• Associated with increased lifetime risk for nicotine dependence	
	• More frequently associated with asthma	
	• Stigmatization more intense and more common in childhood and adolescence	
	• More depression in bariatric surgery candidates	
Thyroid disease	• Three to four times more common	
	• Antithyroid antibodies more prevalent	
	• Increased prevalence of hypothyroidism in particular in old women	
Osteoporosis	• 51% remaining lifetime probability for osteoporotic fractures at the age of 50 years	• 20% remaining lifetime probability for osteoporotic fractures at the age of 50 years
	• Much more common in postmenopausal women	• Higher mortality rate after hip fractures
	• Lower bone mass density and bone size	• Secondary osteoporosis more frequently (alcohol abuse, glucocorticoid therapy, or hypogonadism)
Cushing/adrenal insufficiency	• Cushing's disease preponderance	• Prepubertal Cushing's disease more common
	• More often unspecific symptoms of adrenal insufficiency	• More severe symptoms at clinical presentation and earlier onset

CRP C-reactive protein, *PAI-1* plasminogen activator inhibitor-1, *DM* diabetes mellitus, *PCOS* polycystic ovarian syndrome, *SHBG* sex hormone binding globulin

3.4 Metabolism of Testosterone

Testosterone is the main androgen in men. More than 95% of testosterone is produced by Leydig cells in the testis. The rest of testosterone is produced in the adrenal gland. Androgen is also produced in women's ovaries and adrenal glands. As with female hormones, testosterone secretion is regulated by the hypothalamus-pituitary-gonadal axis. Basically, the secretion and production of testosterone is controlled by a negative feedback (Fig. 3.1).

Most of the testosterone in the blood is bound to proteins such as sex hormone binding globulin and albumin, while only 1–4% of testosterone is free testosterone. Only free testosterone, as most hormones do, has been known to be biologically active, but protein bound testosterone is also capable of transmitting signal into cells and biologically active [23, 25].

3.5 Physiologic Effects of Testosterone

Testosterone is important for the development of male genital organs and reproductive function. Testosterone promotes sperm production in testicular Sertoli cells. The promotion of bone formation and maintaining muscle mass is the main metabolic effects of testosterone. Testosterone enhances differentiation of osteoblasts to mature osteocytes and inhibits apoptosis of these cells to increase bone formation [26]. In large cohort studies, serum testosterone level is significantly correlated with bone mineral density. Testosterone replacement for old men with hypogonadism increased bone mineral density. Another study reported that testosterone treatment increased muscle mass and reduced fat mass [27, 28].

Testosterone plays an important role in hair growth. Interestingly, testosterone makes beards grow, but there is no significant effect on eyebrows, and inhibits the growth of scalp hair. This is called as "androgen paradox." This is because dermal papillae of each body part react differently to testosterone. The dermal papillae of the chin secretes the growth factor (IGF-1), while the dermal papillae of the scalp secretes the growth inhibitor interleukin-6 in response to testosterone [29]. In women with androgen excess, such as congenital adrenal hyperplasia and polycystic ovarian syndrome, hypertrichosis occurs in androgen-responsive areas. Not all the hair on the skin grows in response to androgen, but only the hair on androgen-dependent area grows in response to androgen. Hair loss due to excessive testosterone is characterized by hair loss on the forehead or the top of the head. Interestingly, even the scalp hair reacts differently to testosterone.

Testosterone is known to affect emotions, alleviating the degree of anxiety and depression, and being linked to violence. The tendency that women are less violent and depression is more often in women may be associated with lack of testosterone in women. Testosterone is, sometimes, referred to as a causative agent that creates personality differences between men and women. The relationship between psycho-behavioral traits and testosterone is still controversial [30, 31].

3.6 Effects of Testosterone in the Context of Metabolic Diseases

As mentioned in the previous paragraphs, low testosterone levels increase the risk of type 2 DM and are associated with insulin resistance and dyslipidemia [32]. In large-scale cohort studies, low testosterone was associated with increased overall mortality rate, mainly due to cardiovascular disease [33]. It is not clear how testosterone increases cardiovascular mortality and the prevalence of diabetes. Testosterone treatment for male patients with diabetes has shown improvements in insulin resistance indices. Previous studies showed that obesity rates were high in patients with low testosterone levels, and testosterone treatment for these patients reduced obesity, especially visceral fat [34, 35]. The most notable difference in obesity characteristics between men and women is that visceral obesity is more severe in men, which is linked to chronic inflammation, insulin resistance, and cardiovascular disease. The increase of muscle mass,

which plays an important role in reducing visceral fat and insulin resistance, by testosterone treatment could contribute to improved glucose metabolism and cardiovascular mortality [36] (Fig. 3.4).

Testosterone is converted to dihydrotestosterone by 5α-reductase in hair follicles and prostate, which causes hair loss and prostatic hypertrophy. This leads to the use of 5α-reductase inhibitors in patients with prostate hypertrophy, prostate cancer, and alopecia. When androgen deprivation therapy was used to treat prostate cancer, incidence of diabetes and cardiovascular diseases and cardiovascular mortality increased. Testosterone treatment reduced LDL cholesterol in male patients with hypogonadism and showed additional improvements in lipid metabolism even in patients who were already taking statins. These are the evidence for the metabolic benefits of testosterone [37, 38].

Obesity leads to a decrease in androgen level, and patients with hypogonadism are prone to obesity. The rationale for this is that as adipocyte increases, the activity of aromatase increases, and testosterone is converted to estradiol. This is the basis for a decrease in testosterone levels in obese patients, and it is also known that degradation of testosterone increases the number of fat cells and affect their distribution.

In women, androgen is also produced in adipose tissues and adrenal glands. Although it is a relatively rare disease, congenital adrenal hyperplasia has a defect in the production of steroid hormones in the adrenal gland, which results in the deficiency of cortisol and aldosterone, major adrenal hormones, and increase of androgen production. In women, the increased androgen leads to virilization. However, it is not known whether the increase of androgen in women increases muscle mass and reduces obesity. Rather, considering the higher risk of diabetes and cardiovascular diseases in women with polycystic ovary syndrome, in which androgen is increased, the effect of androgen in women is not expected to be the same as in men. The insulin resistance of polycyclic ovaries promotes the production of

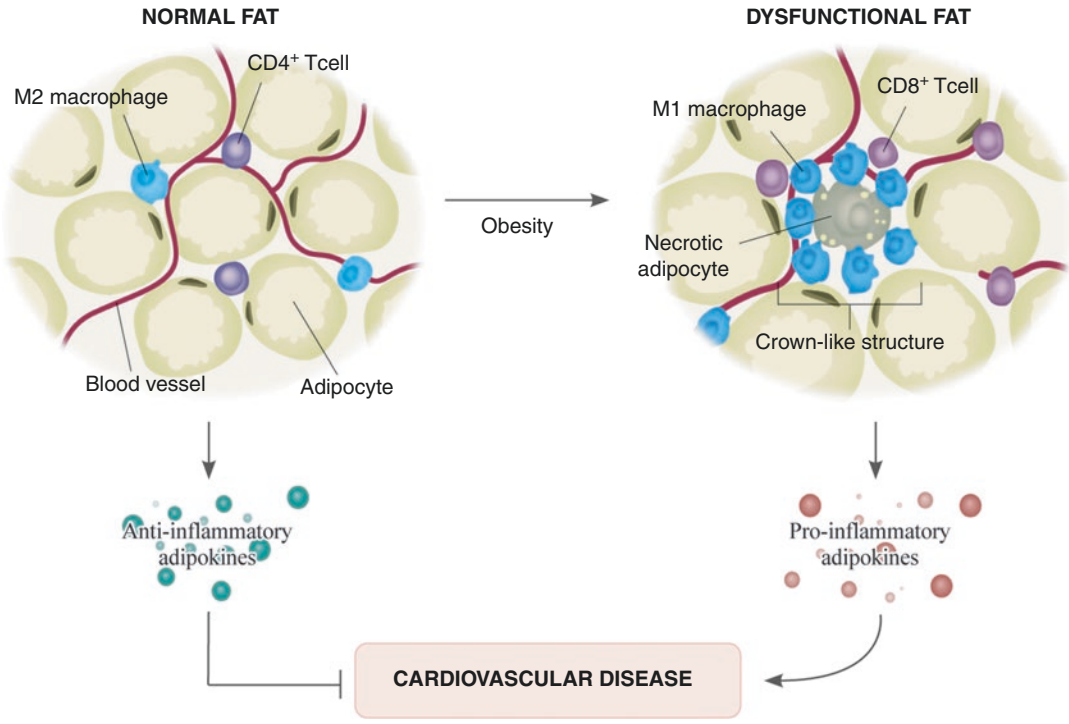

Fig. 3.4 Role of chronic inflammation in adipose tissue for the development of cardiovascular diseases (adapted from Nakamura et al. [36])

androgen, which increases the secretion of LH in the pituitary gland, resulting in a further increase in androgen production. Oral contraceptives are used as a treatment for PCOS to restore the balance of estrogen and testosterone, and metformin, a antidiabetic medication, is used to reduce insulin resistance in PCOS [39].

3.7 Conclusions

Estrogen and testosterone are the main sex hormones that determine the difference between women and men. Majority of estrogen and testosterone are produced and secreted in the ovaries and testis, which is controlled by the hypothalamus-pituitary-gonad axis but can also be partially produced in adipose tissues and adrenal glands. The decrease of estrogen inhibits bone formation and enhances bone resorptions which leads to the progression of osteoporosis. Testosterone is known to contribute to improving insulin resistance and preventing diabetes by reducing visceral fat and increasing muscle mass in men. Conversely, testosterone deprivation therapy and hypogonadism increase obesity, diabetes, and cardiovascular diseases. However, in women with androgen excess, diabetes and insulin resistance paradoxically increased. Further studies are needed on the role of sex hormones in metabolic diseases.

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Part IV

Esophagus

Gastroesophageal Reflux Disease

4

Nayoung Kim

4.1 Introduction

Gastric acid has positive functions such as digestion of proteins, absorption of minerals such as calcium and iron, and sterilization of harmful microorganisms in ingested food. However, gastric acid is very acidic, with a pH of 1–2; therefore, excessive secretion or acid reflux can cause gastroesophageal reflux disease (GERD) and gastric ulcers; as described below, GERD is a spectrum that encompasses reflux esophagitis (RE) and non-erosive reflux disease (NERD). GERD, which is becoming more prevalent, refers to gastric or duodenal content entering the esophagus and causing reflux symptoms or tissue damage in the esophagus, pharynx, larynx, or bronchi. Thick mucus exists in the gastric mucosal surface as a defense mechanism to prevent tissue damage from highly acidic gastric juice (Fig. 4.1a), but this defense mechanism in the esophagus is weak. Therefore, when refluxed gastric acid remains in the esophagus, tissue damage occurs. In countries where obesity is relatively prevalent and the diet is centered on meat rather than vegetables, GERD is highly common—to the point that one out of four people over 60 years old experience GERD—and the incidence of complications such as esophageal adenocarcinoma is high, leading to societal attention on GERD as an important health issue. However, in Asian countries, GERD has not traditionally received much attention since the prevalence was low and the symptoms were mild. However, rapid social changes led to increased stress and lifestyle changes resulting in more widespread consumption of a Westernized diet, obesity, tobacco use, and alcohol drinking. As a result, increasingly many individuals are experiencing epigastric burning sensation, heartburn, epigastric pain, nausea, vomiting, acid reflux, chest pain, sore throat, and digestive problems. These symptoms can be due to ulcers in the stomach or the duodenum, but in light of recent trends, it is more likely that they are due to GERD. The general category of GERD includes structural changes such as RE (Fig. 4.1b), esophageal stenosis, which is a complication of RE (Fig. 4.1c), and Barrett's esophagus (Fig. 4.1d). However, NERD (Fig. 4.2), which does not involve damage to the esophagus, is much more prevalent among females [1]. Functional heartburn is diagnosed in patients with similar symptoms to those of GERD, but without acid reflux, in whom esophageal motility disorder should be ruled out. Functional heartburn does not respond to proton pump inhibitors and is more common among females than among males. However, unless an

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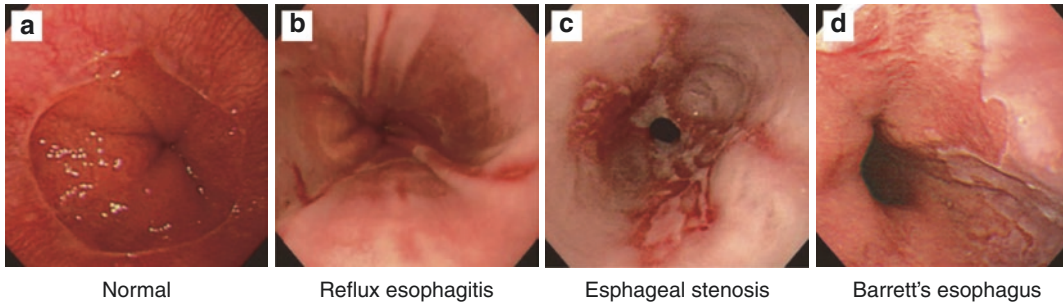

Fig. 4.1 Endoscopic findings of reflux esophagitis, esophageal stenosis, and Barrett's esophagus. (**a**) Normal esophagus, (**b**) reflux esophagitis, (**c**) esophageal stenosis, (**d**) Barrett's esophagus

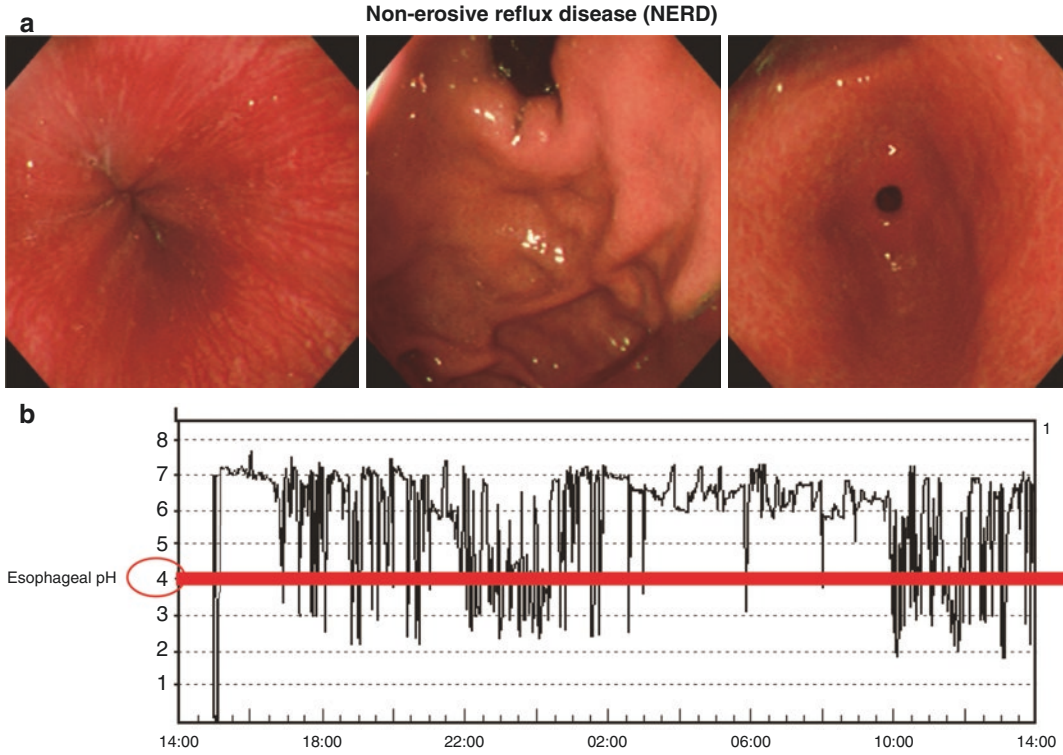

Fig. 4.2 Endoscopic findings of non-erosive reflux disease (NERD) (**a**) and findings from 24-hour ambulatory esophageal pH monitoring (**b**)

esophageal acidity test is conducted, it is difficult to differentiate NERD and functional heartburn. Between these two diagnoses, there are ambiguous cases that are simultaneously acid related and non-acid related. Recently, in Rome IV Criteria, acid hypersensitive esophagus and non-acid hypersensitive esophagus were combined into the concept of reflux hypersensitivity, which is positioned between NERD and functional heartburn [2]. RE, where the esophageal mucosal tissue damaged by acid reflux can be observed endoscopically (Fig. 4.1b), has been reported to be 3.61 times [1] or 2.28 times [3] more common in males than in females, and sex/gender differences have been found in the disease mechanism, symptoms, and response to medication [4, 5]. In the Western literature, it has been reported that GERD progresses into esophageal stenosis (Fig. 4.1c), Barrett's esophagus (Fig. 4.1d), or—rarely—esophageal adeno-

carcinoma, but the prognosis is not bad in Asian countries including South Korea. In addition, in the United States, it has been reported that GERD is the most prevalent gastrointestinal disease and is associated with the highest direct spending, as GERD-related expenditures exceed those for peptic ulcers, chronic inflammatory bowel disease, and colon cancer [6]. In this review, the sex/gender differences in the epidemiology, mechanism, symptoms, and response to treatment of GERD are approached from the perspective of sex/gender-specific medicine [7].

4.2 Epidemiology of Gastroesophageal Reflux Disease

Traditionally, functional gastrointestinal disorders (FGIDs) including functional heartburn, functional dyspepsia (FD), and irritable bowel syndrome (IBS) are known to be more common among women. One might assume that GERD is also more common among women, but the epidemiology of RE due to acid corrosion and NERD is different. Therefore, when evaluating the prevalence of GERD, it is reasonable to distinguish GERD studies that only observed symptoms from studies that suggested the presence of RE by conducting endoscopy [7].

4.2.1 Population-Based Studies

According to a study that analyzed GE reflux symptoms (heartburn or acid reflux symptoms at least once a week) without conducting endoscopy, there were no sex/gender differences in the prevalence of GERD. For example, the prevalence in studies on the PubMed database from 1997 to 2011 was 19.4% ± 2.3% in men and 18.9% ± 2.4% in women ($p = 0.87$) [8]. In a study that was conducted in Asan, South Korea, no differences were observed with a prevalence of 3.5% in both genders [9]. The prevalence of GERD was 2.6% in men and 2.4% in women in a 2005 study conducted in the southern region of China, corresponding to no significance difference [10]. No meaningful difference was found (15% in men and 14% in women) in a study conducted in Olmsted County, United States, where obesity is common and GERD is more prevalent [11]. The prevalence was higher among women (14.1%) than among men (9.5%) in a study conducted in Argentina, but the difference was not statistically significant ($p = 0.21$) [12].

4.2.2 Endoscopy-Based Studies

In contrast, studies that measured the prevalence of RE using endoscopy consistently reported a significantly higher prevalence among males than among females [7]. In a 2005 South Korean multicenter study that included 25,536 individuals from 40 medical check-up centers, the prevalence of RE was much higher among men (11.2%) than among women (3.1%) ($p < 0.001$) [1] (Fig. 4.3). In a 2011 multicenter study that included 4023 individuals from 8 medical check-up centers, the prevalence was 2.28 times higher among men (11.4%) compared to that among women (5.0%) [2]. A study with 67,056 individuals included in studies in the PubMed database from 1997 to 2011 also indicated that the prevalence was 2.61 times higher among men (15.9% ± 2.5%) than among women (6.1% ± 1.6%) ($p < 0.01$) [8]. The severity of RE was also significantly greater in men than in women [13]. Conversely, most studies on NERD found a significantly higher prevalence among women [1, 14]. The frequency and severity of symptoms were also higher among women than in men [14–16], indicating a trend opposite of that of RE (Fig. 4.3).

4.3 Pathophysiology of Gastroesophageal Reflux Disease

The mechanism of GERD is as follows. An elastic muscle, known as the lower esophageal sphincter (LES), between the esophagus and the stomach acts as a latch. It relaxes to open when food is ingested and closes after the food passes to prevent acid reflux. RE occurs when the pressure of the LES decreases, transient LES pressure is frequent, and the refluxed gastric content is not

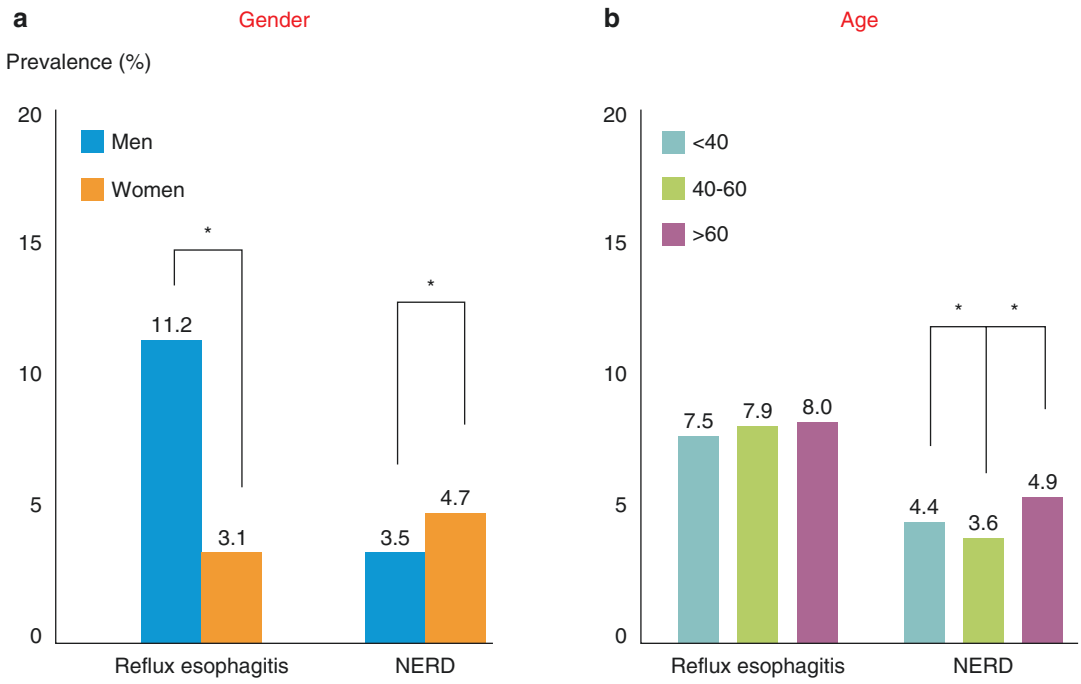

Fig. 4.3 Comparison of reflux esophagitis and non-erosive reflux disease by gender (**a**) and age (**b**). * $p < 0.01$. (adapted from Kim et al. [1])

properly cleaned and remains in the esophagus for a long time. Symptoms are more important for NERD than for RE; therefore, while the LES is important as a structural factor, the anti-inflammatory effect of estrogen, which is involved in the protection of esophageal mucosa cells, the increased expression of tight junction proteins, and symptom sensitivity are more important. When the gaps at intercellular junctions widen and tissue resistance is reduced, gastric acid (H^+) enters through the gaps and stimulates neuroreceptors. The brain then perceives the symptoms due to visceral hypersensitivity, and the symptoms become stronger when the muscles are contracted through the reflex arc [17] (Fig. 4.4). Until recently, factors related to direct erosion of the mucous membrane, such as gastric acid secretion and LES pressure, were emphasized in explaining GERD. However, with increasing recognition that NERD is distinct from RE, is more common, and has a different disease mechanism, aspects of sex/gender-specific medicine such as estrogen factor are being emphasized.

4.3.1 Anti-inflammatory Effect of Estrogen on the Esophagus

As RE is more prevalent among men than women, but the prevalence and severity among women after menopause with increasing severity, estrogen has been identified as a protective factor of the esophagus [18, 19] (Fig. 4.5). This finding is supported by a study on the association between menopause and RE with around 10,000 individuals who received health check-ups. As time passes after menopause, body mass index (BMI), symptomatic GERD, and RE were found to increase. At 20–29 years after menopause, RE increased dramatically [20] (Fig. 4.6). The anti-inflammatory role of estrogen has been suggested in animal studies [7, 21]. In mouse models of chronic RE, estrogen protected esophageal mucosa and externally introduced nitric oxide (NO) caused neutrophil and lymphocyte infiltration and damaged the esophageal mucosa in male mice; however, the damage was reported to be minimal in female mice [22]. Esophageal inflammation was more severe among female mice that underwent

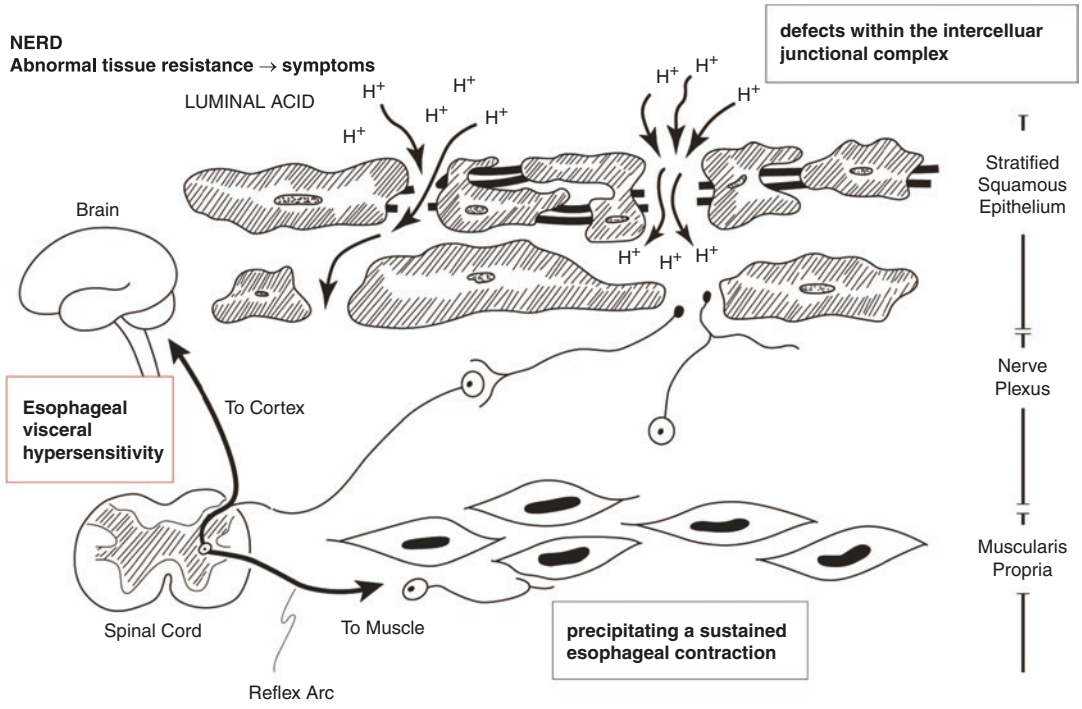

Fig. 4.4 Pathophysiology of non-erosive reflux disease (adapted from Barlow and Orlando [17])

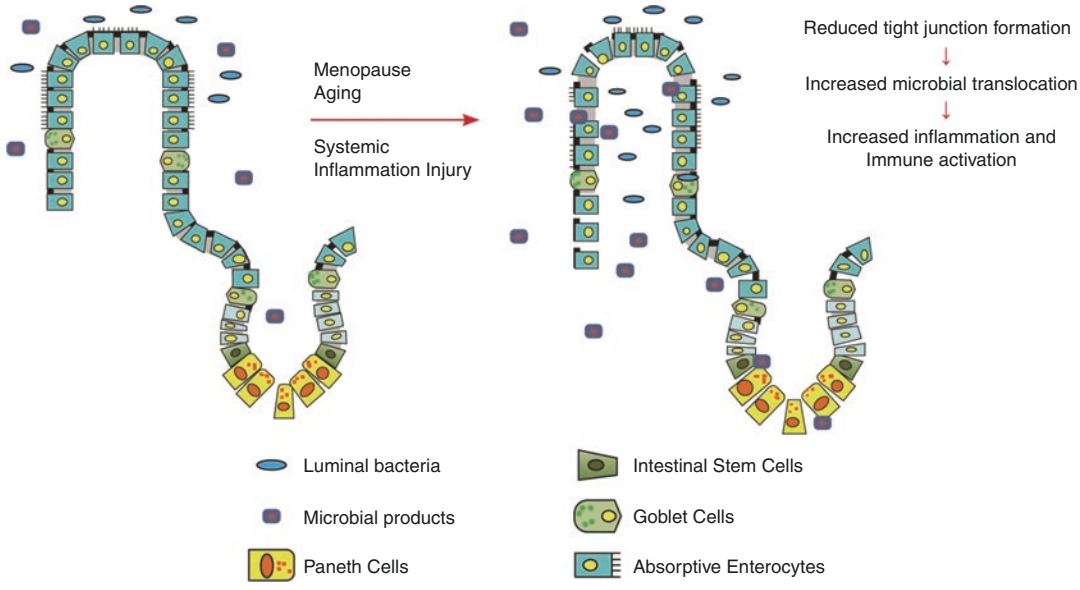

Fig. 4.5 Factors that influence esophageal damage and recovery such as gender, age, and hormones (adapted from Grishina et al. [19])

ovariectomy, but when they and male mice were injected with 17β-estradiol, esophageal damage was reduced as cell toxicity from mast cells, and the secretion of cytokines such as tumor necrosis factor-alpha decreased [22]. When 17α-estradiol was injected, a protective effect was not observed,

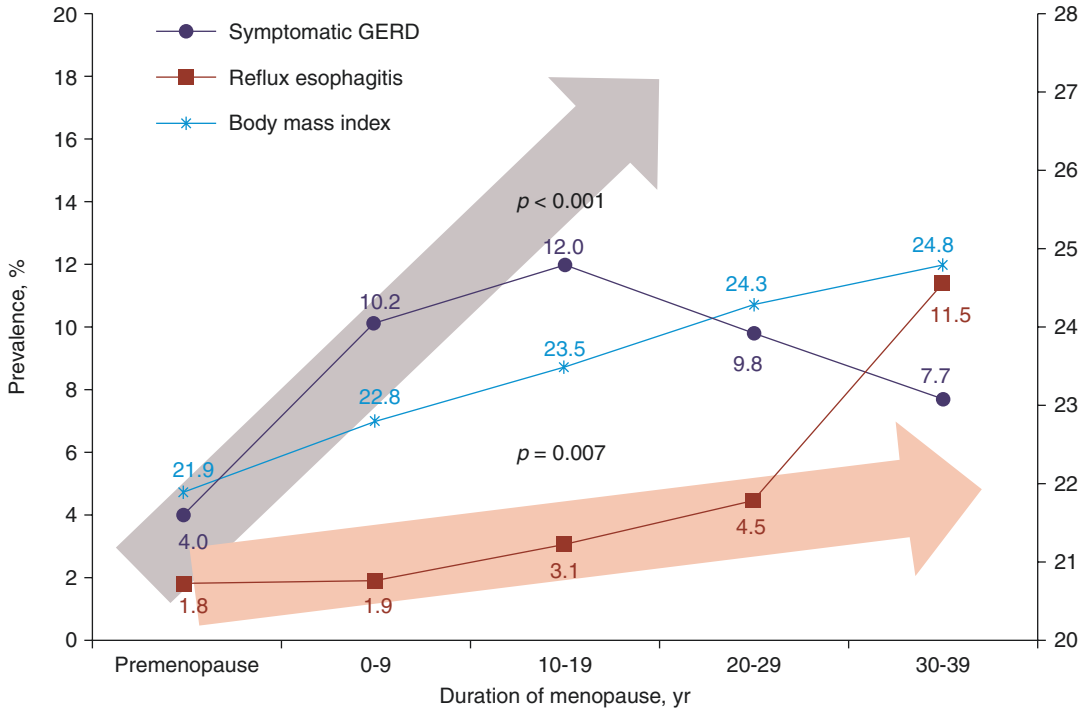

Fig. 4.6 Association between menopause and reflux esophagitis. The finding that body mass index (BMI), symptomatic GERD, and reflux esophagitis (RE) increase with time after menopause and that RE increases dramatically 20–29 years after menopause in around 10,000 individuals who received regular health check-up supports the hypothesis that estrogen is a protective factor against RE (adapted from Kim et al. [20])

indicating the importance of specifically 17β-estradiol [22]. In addition, estrogen was also found to suppress esophageal macrophage migrating inhibitory factor (MIF) [23]. The low prevalence of RE among females is explained by this finding as estrogen downregulates MIF when wounds are healed [7, 24].

4.3.2 Protective Function of the Esophageal Epithelium

If the protective function of the esophageal epithelium is strong, esophageal tissue will not be damaged even when subjected to noxious stimuli such as gastric acid and bile reflux. RE is prevalent in men, who have low estrogen levels, and menopausal women because estrogen promotes the expression of tight junction proteins that close gaps between cells and prevents esophageal mucosa permeability and bacterial migration [19, 25] (Fig. 4.5). When 17β-estradiol was injected into rabbits for 2 weeks and an Ussing chamber experiment was performed after removing the esophagus, those treated with 17β-estradiol demonstrated decrease of cell permeability from stimulants such as gastric acid through enhanced occluding expression [25]. In an analysis of the endoscopy data of 45 patients with RE, 14 patients with NERD, and 16 healthy volunteers conducted by our team, the level of occludin mRNA was lower in male RE patients than in healthy male participants, but there were no changes in the expression of tight junction proteins in female RE patients [16].

4.3.3 Nociception

An important mechanism when sensing symptoms such as heartburn from acid reflux is visceral hypersensitivity due to the transient

receptor potential vanilloid-1 (TRPV1), which is distributed in the esophageal mucosa [26–28]. When gaps in the intercellular junction of the esophageal mucosa widen and tissue resistance is reduced, gastric acid (H^+) enters through the gaps and stimulates TRPV1. The brain then perceives symptoms due to visceral hypersensitivity [17, 29]. It was reported that esophageal mucosa TRPV1 was expressed more in individuals who experienced GERD symptoms than in those who did not have GERD symptoms and that TRPV1 expression was higher among NERD patients than among RE patients [30, 31]. Some studies have connected TRPV1 directly to inflammation. In a study by our team, TRPV1 and proteinase-activated receptor 2 (PAR2) were more activated in RE patients than in NERD patients [26], and TRPV1 and PAR2 were directly related to inflammation and esophageal reflux symptoms but were not related to extraesophageal symptoms [26]. These findings demonstrate that TRPV1 activation is closely related to the main symptoms of GERD, since it causes inflammation in the cells and nerves by increasing the secretion of substance P in primary afferent neurons and calcitonin gene-related peptide (CGRP) [32] and causes heartburn [30]. In contrast, in patients who had 24-hour ambulatory esophageal pH monitoring after experiencing heartburn, the number of reflux with a pH less than 4 and the duration of reflux were smaller and shorter among female patients than among male patients [33]. This result indicates that a potential reason why NERD is more common among women may relate to the visceral hypersensitivity mechanism after being exposed to weak acid.

4.3.4 Psychological and Emotional Factors

The fact that psychological and emotional factors are very important in the experience of GERD symptoms such as heartburn is well-known [34, 35]. In both RE and NERD, acute stress significantly increases the hypersensitivity toward gastric acid. It was found that emotional responses to the cause of stress and symptom experiences were related [36]. In the general population, depression and anxiety are more common among women than among men [37] and NERD is more common in women who have depression or anxiety. It is clear that depression and anxiety influence NERD [38]. It has been hypothesized that in women who show higher depression and anxiety than men and experience severe GERD symptoms without endoscopic findings, their condition is related to afferent signals, hormones, and the severity of GERD [39, 40]. In addition, the quality of life (QoL) of GERD patients was found to be highly associated with psychological and emotional factors [41], and compared to male GERD patients, QoL dropped significantly more among female GERD patients, who experienced sleep disorders and eating problems [16]. The risk of sleep disorders and anxiety was higher and QoL was lower among patients with NERD, which is more prevalent among women, than among patients with RE, and the GERD impact scale score was also significantly higher in the NERD group (9.2 ± 0.4) compared to the score in the RE group (6.5 ± 0.3) ($p < 0.001$) [41]. Moreover, NERD patients experienced difficulty in their daily routines and had high anxiety measured by the Hospital Anxiety and Depression Scale (HADS) [41].

The experience of NERD symptoms is crucially linked to visceral hypersensitivity, for which peripheral sensitization, central sensitization, and psychoneuroimmune interactions are important [28, 42–44] and the brain-gut axis plays an important role, which is crucial in the symptom experience of NERD. When the central (through brain-gut interactions) and peripheral sensitization mechanisms cause stimulation in the esophagus, perception becomes more sensitive, which causes the symptoms of NERD [37]. In summary, sensitivity to gastric acid is more important than physical damage due to gastric acid for NERD, which is more common among women.

4.3.5 Comparison of Risk Factors by Type of Gastroesophageal Reflux Disease

The risk factors of RE and NERD can be understood in relation to their pathophysiology. In a South Korean study with 25,536 participants (15,180 males and 10,356 females), the risk factors of RE and NERD were very different [1]. A multivariate analysis of risk factors of RE showed that male sex, alcohol consumption, hiatal hernia, treatment of *Helicobacter pylori* (*H. pylori*), and BMI greater than 25 kg/m^2 were risk factors, while *H. pylori* positivity was a protective factor (Table 4.1 and Fig. 4.7a). In contrast, female sex, tobacco use, age under 40 or over 60, BMI lower than 23 kg/m^2, antibiotics use, slouched work posture, and average monthly income below 1000 dollars were significant risk factors for NERD [1] (Table 4.2 and Fig. 4.7b). In a Japanese study with 10,837 individuals who received health check-ups (6332 males and 4505 females), the risk factors of RE were male sex, old age, alcohol use, tobacco use, no *H. pylori* infection, a high pepsinogen I/II ratio, and high BMI [14]. The risk factors of NERD were female sex, young age, tobacco use, alcohol use, *H. pylori* infection, a high pepsinogen I/II ratio, and high BMI [14]. In a 2011 study with 4023 individuals who received health check-ups in South Korea (2087 males and 1082 females), risk factors of RE were no *H. pylori* infection (odds ratio [OR] 1.91; 95% confidence interval [CI], 1.48–2.46), BMI ≥ 25 kg/m^2 (OR 1.49; 95% CI, 1.08–2.06),

Table 4.1 Multivariate analysis of risk factors of reflux esophagitis in a 2006 national epidemiological survey (sample size = 25,536) (adapted from Kim et al. [1])

Variable	Normal (n = 20,154)	Reflux esophagitis (n = 1810)	Odds ratio	95% CI
Male (%)	11,401 (56.6)	1633 (84.2)	3.00	2.26–3.98
Alcohol consumption (%)	7681 (38.1)	1050 (58.0)	1.48	1.21–1.81
Body mass index ≥ 25 (%)	6523 (29.8)	757 (41.8)	1.28	1.05–1.55
Hiatal hernia ≥ 1 cm (%)	383 (1.9)	212 (11.7)	5.40	3.73–7.70
H. pylori eradication history (%)	1572 (7.8)	223 (12.3)	2.20	1.60–2.75
H. pylori-positive (%)	12,173 (60.4)	832 (46.0)	0.47	0.39–0.58
Glucose ≥ 126 mg/dl (%)	987 (4.9)	119 (6.6)	1.06	0.78–1.45
Triglyceride 150 mg/dl (%)	4655 (23.1)	653 (36.1)	1.15	0.94–1.41
Smoking (%)	4655 (23.1)	795 (41.0)	1.19	0.98–1.45
Medication for liver disease (%)	504 (2.5)	65 (3.6)	1.07	0.75–1.47
Medication for heart disease (%)	2096 (10.4)	250 (13.8)	1.09	0.79–1.50

CI confidence interval

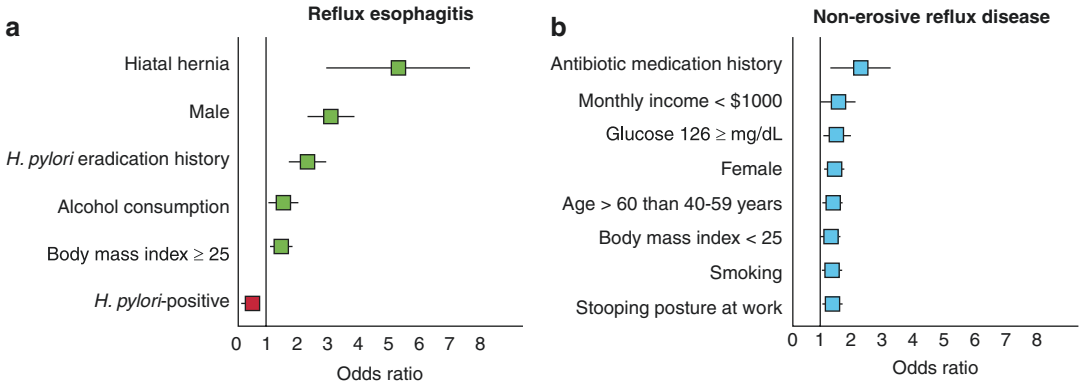

Fig. 4.7 Multivariate analysis of risk factors of reflux esophagitis (**a**) and non-erosive reflux disease (**b**) (adapted from Kim et al. [1])

Table 4.2 Multivariate analysis of risk factors of non-erosive reflux disease (NERD) in the 2006 national epidemiological survey (sample size = 25,536) (adapted from Kim et al. [1])

Variable	Normal (n = 20,154)	NERD (n = 996)	Odds ratio	95% CI
Female (%)	8753 (43.4)	480 (48.2)	1.29	1.10–1.50
Age below 40 than 40–59 years	5502 (27.3)	299 (30.0)	1.24	1.06–1.45
Age ≥ 60 than 40–59 years (%)	3003 (13.7)	170 (17.1)	1.25	1.02–1.54
Body mass index < 23 (%)	8384 (41.6)	498 (50.0)	1.22	1.06–1.41
Monthly income < $1000 (%)	1632 (8.1)	120 (12.0)	1.37	1.06–1.69
Glucose ≥126 mg/dl	987 (4.9)	82 (8.2)	1.34	1.04–1.73
Antibiotic medication history (%)	198 (1.0)	23 (2.3)	2.07	1.28–3.34
Smoking (%)	4655 (23.1)	270 (27.1)	1.21	1.03–1.43
Stooping posture at work (%)	3396 (16.9)	230 (23.0)	1.19	1.06–1.69
H. pylori eradication history (%)	1572 (7.8)	103 (10.2)	1.25	0.99–1.57
Hiatal hernia ≥ 1 cm (%)	383 (1.9)	30 (3.0)	1.14	0.76–1.70
Medication of NSAIDs (%)	1380 (6.8)	86 (8.6)	1.25	0.97–1.62

NERD non-erosive reflux disease, *CI* confidence interval

triglycerides ≥150 mg/dL (OR 1.65; 95% CI, 1.08–1.06), fasting blood glucose ≥126 mg/dL (OR 1.72; 95% CI, 1.06–2.81), and esophagus hiatal hernia (OR 3.10; 95% CI, 1.86–5.16). Residence in a large city was a protective factor (OR 0.59; 95% CI, 0.39–0.90) [2].

4.4 Symptoms of Gastroesophageal Reflux Disease

The following symptoms are characteristic of GERD. The first and second symptoms are classified as esophageal symptoms, and the third through fifth symptoms are classified as non-esophageal symptoms.

(a) Heartburn that is felt in the back of the sternum or substernal burning.
(b) Reflux symptoms where gastric juices or stomach context refluxes into the pharynx. Patients generally describe a sour and bitter taste. This symptom tends to occur after eating large quantities of food or lying down immediately after eating.
(c) Excessive salivation, dysphagia, and swallowing pain due to stimulation from gastric acid.
(d) Chronic laryngeal symptoms, throat discomfort (expressed as something stuck in the throat or uneasiness), coughing, and hoarseness.
(e) Stinging sensation in the chest or chest pain similar to pain experienced due to coronary artery disease.

It was assumed that these symptoms are experienced when there is RE, but as endoscopy became more widespread as part of health check-ups, it was found that 50% of patients with RE do not feel any symptoms [1]. In addition, there were sex/gender differences in reflux symptoms. Among patients who visited gastroenterologists and received an RE diagnosis after gastroscopy, the proportion of patients with GERD symptoms was much higher among female patients, with 86.4% among female patients and 56.5% among male patients [16]. Heartburn, gastric acid reflux, and chest pain were found to be more common among females; while 100% of females reported throat discomfort, only 28.6% of males reported this symptom [16]. A probable explanation for this difference is that females have a lower pain tolerance, but pain tolerance did not differ by body size or the diameter of the esophagus in both sexes [45]. When there is a burning sensation in the back of the sternum, burning or heating sensation, and pain (similar to GERD symptoms), without evidence of reflux and with the exclusion of esophageal motility disorder, the symptoms are labeled as functional heartburn. If GERD is viewed as a spectrum, on one extreme, there is Barrett's esophagus that entails severe tissue damage, followed by RE, NERD where

tissue damage is not observed, and functional heartburn. Exposure to noxious gastric content is greatest in Barrett's esophagus, but esophageal sensitivity is greatest in functional heartburn [46] (Fig. 4.8). Functional heartburn is more prevalent among females and they do not improve after using proton pump inhibitors (PPIs) since the symptoms are not caused by gastric acid reflux. Taken together, sex/gender should be accounted for in the approach to treatment for symptoms that indicate GERD.

4.4.1 Differences in Esophageal and Extraesophageal Symptoms by Sex/Gender

Esophageal symptoms such as heartburn and gastric acid reflux are related to inflammatory markers such as TRPV1, PAR2, and IL-8, but extraesophageal symptoms are not related to these inflammatory markers [16]. This indicates that esophageal symptoms occur as a result of inflammation in response to gastric acid exposure in the distal esophagus, but extraesophageal symptoms are related to vasovagal reflex due to gastric acid exposure in the distal esophagus [16]. An interesting study found that 87.5% and 12.5% of RE patients reported esophageal symptoms and extraesophageal symptoms, respectively, as their main symptom, while 61.3% and 38.7% of NERD patients reported esophageal symptoms and extraesophageal symptoms, respectively, as their main symptom. NERD patients, unlike RE patients, have a high proportion of extraesophageal symptoms [3].

In a study where endoscopy, esophageal manometry, and 24-hour ambulatory esophageal pH monitoring were analyzed comprehensively, heartburn, gastric acid reflux, and nighttime symptoms were significantly more frequent in females than in males [15]. Among females, diarrhea, epigastric pain, and constipation symptoms were also more common ($p < 0.01$) beyond GERD symptoms, indicating a sex/gender difference in how patients experience and report symptoms [15]. According to a phone survey conducted in Brazil, females reported the symptom of acid reflux more than twice a week 1.5 times more frequently than males. Heartburn ($p = 0.047$), burning in the substernal area ($p = 0.012$), acid reflux ($p < 0.001$), dysphagia ($p = 0.012$), and swallowing pain ($p = 0.009$) were all more common in females than in males [47]. This finding showed

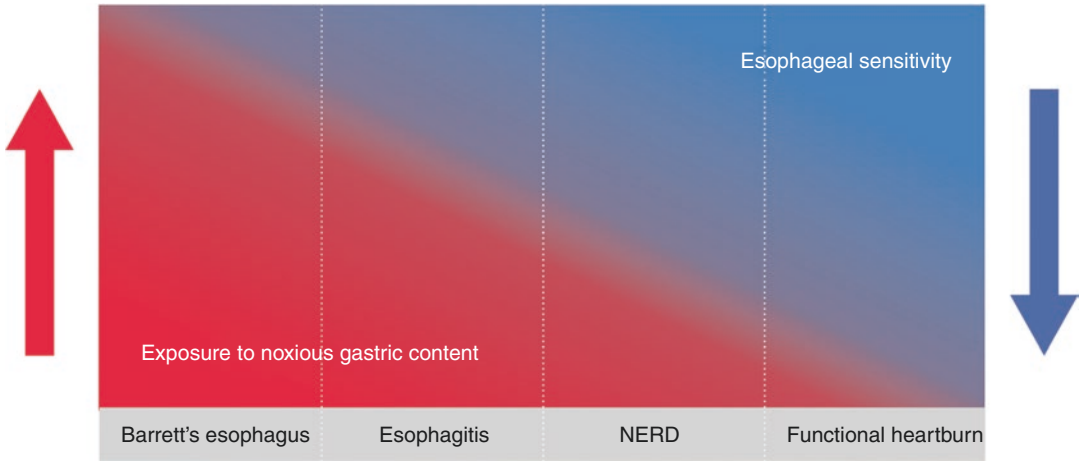

Fig. 4.8 Gastroesophageal reflux disease (GERD) spectrum and the relationship between tissue damage and esophageal sensitivity. GERD can be classified into Barrett's esophagus, which entails severe tissue damage, reflux esophagitis (RE), non-erosive reflux disease (NERD) (where tissue damage is not observed), and functional heartburn. Exposure to noxious gastric content is greatest in Barrett's esophagus, and esophageal sensitivity is greatest in functional heartburn (adapted from Weijenborg and Bredenoord [46])

that sex/gender differences in GERD symptoms are a universal phenomenon. A report that extra-esophageal symptoms were more frequent in females than in males (OR 1.15; 95% CI, 1.03–1.30; $p < 0.0178$) [48] can be interpreted in a similar context. In addition, depression and anxiety symptoms were also more common among females than among males [38].

4.4.2 Differences in Frequency of Healthcare Usage by Sex/Gender

Differences by country or culture can exist, but it has been reported that when it comes to GERD, females take the symptoms more seriously and visit medical institutions faster [49, 50]. A similar finding was reported in a community-based study in China [51]. Factors associated with frequent healthcare visits were female sex ($p < 0.001$), frequency of heartburn ($p = 0.032$), depression ($p = 0.004$), and social morbidity ($p < 0.001$) [51]. Some hypothesize that as females receive more tests to find the cause of the symptoms and actively seek out endoscopic treatment or surgery, Barrett's esophagus and esophageal adenocarcinoma are less common among females [15].

4.5 Treatment of Gastroesophageal Reflux Disease

GERD is a chronic disease, and the established consensus is that patients' pain should be reduced as much as possible through drug treatments along with changes in dietary habits including limiting tobacco, alcohol, coffee, and tea, which promote reflux, as well as lifestyle changes [52, 53]. The main focus of drug treatment is to reduce secretion of gastric acid and minimize damage in the esophageal mucosa due to gastric acid. Common drugs for this purpose are PPIs and histamine H_2 receptor antagonists (H_2RAs). Proton pump inhibitors are more effective than H_2RAs and are therefore selected as the first-line drug for GERD. However, 36.4% of GERD patients were not satisfied with the treatment result after 8 weeks of PPI use. Satisfaction was especially low among Koreans at 42.9% [54], and factors associated with low satisfaction were female sex, NERD, depression/anxiety, low BMI, irritable bowel syndrome, and geography (Asia and Australia) [54] (Table 4.3). Most factors were related to sensitivity toward gastric acid such as visceral hypersensitivity. Recently, potassium-competitive acid blockers (P-CABs), such as tegoprazan and vonoprazan, which address the disadvantages of PPIs such as acid night breakthrough, have been developed and are expected to improve treatment satisfaction among female patients, NERD patients, and patients with extraesophageal symptoms. This review briefly discusses the reasons for sex/gender differences in drug treatment responses.

Table 4.3 Factors associated with poor symptom improvement response to proton pump inhibitors in GERD (adapted from Heading et al. [54])

Factor	Logistic regression *p*-value
ERD/NERD	<0.0001
HADS total score	<0.0001
Anxiety sub-score	<0.0001
Depression sub-score	<0.0001
IBS	<0.0001
BMI	<0.0001
Gender	0.0011
Geography	0.0052
H. pylori	Not significant
Age	Not significant
Esophagitis grade (A–D)	Not significant

4.5.1 Drug Response and Sex/Gender

PPIs are the most important drug for GERD [55], but 17–32% of GERD patients report heartburn and acid reflux symptoms that continue to reduce their QoL despite treatment with PPIs at the standard dose. They also report GERD symptoms that do not respond to higher doses of PPIs [56]. Sex/gender has been reported to be a very important factor associated with nonresponse to PPIs [38, 54, 56–58]. In a study of GERD patients

newly diagnosed in primary care facilities, incomplete response to PPIs was more common among females (OR 1.20; 95% CI, 1.05–1.37) [57], which was confirmed by a systematic review. Females more frequently reported continuing symptoms despite treatment with PPIs than males (risk ratio [RR] 3.66; $p < 0.001$) [58]. In contrast, a study limited to RE with frequent heartburn found that symptom improvement from PPI use was better in males than in females (OR 1.35; 95% CI, 1.14–1.59; $p < 0.001$) [59]. In a study by the author with 100 NERD patients and 71 RE patients, factors associated with poor response to PPIs were BMI < 23 kg/m^2 (OR 2.20; 95% CI, 1.12–4.34), having received psychiatric treatment or taking psychiatric medication (OR 2.44; 95% CI, 1.23–4.85), a high Pittsburgh Sleep Quality Index score (assessment of sleep quality) (OR 1.20; 95% CI, 1.05–1.35), and NERD (OR 3.30; 95% CI, 1.54–7.11). There was no significant sex/gender difference ($p = 0.91$) [4]. This finding may be due to the small sample size or the possibility that GERD symptoms were severe in both males and females who visited a tertiary hospital. In a larger study with 5796 patients with either RE or NERD, female sex was associated with an increased dose of PPIs [60]. In a 5-year post hoc test of the LOTUS trial, factors associated with an increase of the esomeprazole dose from 20 mg to 40 mg per day were female sex, tobacco use, no *H. pylori* infection, a long history of GERD, and high gastric acid reflux into the esophagus when lying down ($p < 0.05$ for all) [61]. In 683 GERD patients excluding functional heartburn patients using 24-hour ambulatory esophageal pH monitoring, the conditions associated with good response to PPIs were male sex, obesity, typical esophageal symptoms such as heartburn and reflux, and alcohol use [62]. In summary, patients who respond well to PPIs are those whose symptoms are directly caused by gastric acid reflux, and patients who do not respond well to PPIs are those with NERD, those who are sensitive to gastric acid due to visceral hypersensitivity (as is common among female patients), and those with functional heartburn [2].

4.5.2 Effects of Hormone Therapy for Gastroesophageal Reflux Disease

Estrogen has anti-inflammatory properties and is known to regulate aspects of immune system activation, such as cytokines and wound healing [19], indicating the possibility that estrogen may be protective against GERD [63]. In postmenopausal women, taking estrogen can prevent mucosa damage due to gastric acid reflux and suppress the progression to Barrett's esophagus or esophageal adenocarcinoma [63]. In a case-control cohort study, consistent hormone therapy over 5–10 years reduced esophageal adenocarcinoma (hazard ratio [HR] 0.25; 95% CI, 0.07–0.95), and the risk reduction was proportional to time (HR 0.06; 95% CI, 0.01–0.43) [63]. However, it has also been reported that female sex hormones increase gastric acid reflux by relaxing the lower esophageal sphincter through nitric oxide [64, 65]. A community-based study found that hormone therapy was associated with reflux symptoms, which were worse when patients' BMI was >35 kg/m^2 than when it was <25 kg/m^2 in both males (OR 3.3; 95% CI, 2.4–4.7) and females (OR 6.3; 95% CI, 4.9–8.0) [66]. These conflicting results indicate that more studies are needed.

4.6 Conclusions

GERD can be categorized into RE, where the esophagus is damaged, and NERD, in which GERD symptoms occur without damage in the esophagus. RE is 3.51 times more common in males than in females, while NERD is 1.35 times more common in females than in males. RE is more common in males due to structural factors such as the lower esophageal sphincter, the anti-inflammatory effect of estrogen that is involved in the protection of esophageal mucosa cells, and under-expression of tight junction proteins. Visceral hypersensitivity to gastric acid, rather than physical damage from gastric acid, is more important for NERD, which is more common in

females. Heartburn, gastric acid reflux, and chest pain are more common among females, and there was a significant difference in throat discomfort, as 100% of females reported this symptom, versus only 28.6% in males. The most plausible explanation for this difference is that females have a lower pain tolerance. Females respond more poorly to PPIs than males; the reason for this is most likely that females' esophageal mucosa is more sensitive due to visceral hypersensitivity rather than gastric acid itself, meaning that their response to PPIs is relatively weak. Therefore, in order to deliver tailored therapy, an approach that considers sex/gender differences in the pathophysiology of GERD and its response to PPIs is necessary.

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Esophageal Motility Disorders

5

Ju Yup Lee

5.1 Introduction

The esophagus consists of three functional parts: the upper esophageal sphincter (UES), the esophageal body, and the lower esophageal sphincter (LES). Esophagus muscles include striated muscles and smooth muscles. The proximal esophagus, including the UES, comprises striated muscles, which are voluntary muscles. In the distal esophagus including the LES, smooth muscles, which are involuntary muscles, are present. Both smooth and striated muscles are distributed between the proximal esophagus and the distal esophagus. The outer layer of the esophagus consists of longitudinal muscles, with orbicular muscles observed in the inner layer. Motility of these esophageal muscles is controlled by intrinsic innervation of the esophagus and extrinsic innervation by the central nervous system, which results in peristalsis from the proximal to distal esophagus. The harmony between contraction and relaxation of esophageal muscles is important in the motility physiology of the esophagus. Esophageal motility disorders are caused by alterations in normal physiological movements of the esophagus or by disorders in incongruity of esophageal motility [1–3] (Fig. 5.1).

Diseases of the UES and cervical esophagus are caused by abnormal sequential excitation by extrinsic nerves or by diseases involving striated muscles. Movements of these esophageal parts are completely dependent on extrinsic nerves. The pathophysiology of disorders of the lower esophagus and LES can be largely divided into two categories: hypomotility and hypermotility. Both motility disorders are often accompanied by changes in propagation speed or disharmony in esophageal motility.

Hypomotility of the esophagus is caused by abnormalities in smooth muscles that result in no response to neurological excitation, decreased neurogenic excitability, or excessive activity of inhibitory nerves such as non-adrenergic and non-cholinergic neurons. In contrast, hypermotility of the esophagus is caused by abnormalities in smooth muscles, hypersensitivity to neurotransmitters or hormones, or a decrease in the function of inhibitory nerves. Additionally, esophageal disharmony is caused by disorders in non-adrenergic and non-cholinergic nerves. These nerves can gradually delay the contraction of the esophagus toward the lower esophagus to induce peristalsis. Disruption of their functions can result in impaired peristalsis of the esophagus [4, 5].

In the recent version 4.0 [6] of the Chicago Classification based on high resolution manometry

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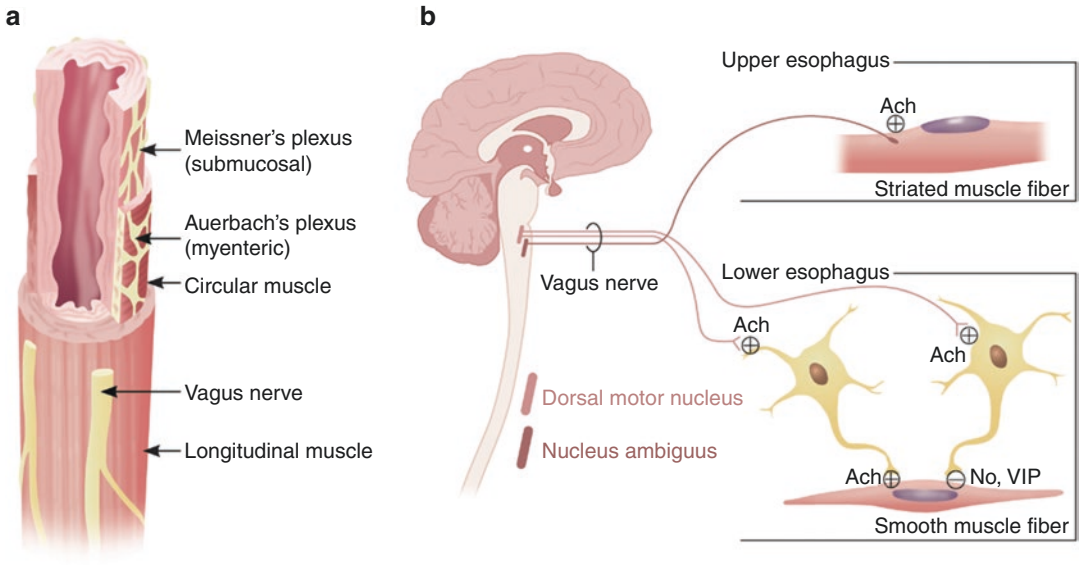


Fig. 5.1 (**a**) Esophageal motor innervation by the vagus nerve, Auerbach's plexus, and Meissner's plexus. (**b**) The striated muscle of the proximal esophagus is directly innervated by somatic efferent cholinergic fibers of the vagus nerve originating from the nucleus ambiguus. In contrast, smooth muscles of the distal esophagus are innervated by preganglionic vagus nerve fibers from the dorsal motor nucleus. Preganglionic vagal fibers can release acetylcholine, a neurotransmitter that affects two types of postganglionic neurons in the myenteric plexus: excitatory cholinergic neurons and inhibitory nitrinergic neurons. *NO* nitric oxide, *VIP* vasoactive intestinal polypeptide (adapted from Ates et al. [3])

(HRM) is a revision of version 3.0 [7], "disorders of esophagogastric junction (EGJ) outflow" are classified as achalasia and EGJ outflow obstruction (EGJOO), while "disorders of peristalsis" are classified as absent contractility, distal esophageal spasm (DES), hypercontractile esophagus, and ineffective esophageal motility [8] (Fig. 5.2).

This chapter will discuss the pathophysiology and diagnosis of esophageal motility disorders and review achalasia and lower esophageal hypermotility disorders as representative esophageal motility disorders. Sex/gender differences of these diseases are also discussed.

5.2 Main Point

5.2.1 Achalasia

Achalasia is a representative primary esophageal motility disorder characterized by incomplete relaxation of the LES and a loss of peristalsis in the esophageal body during swallowing. Achalasia has been named by adding the prefix "a," which means "no" to the Greek word "khalasis" meaning "relaxation" [9].

5.2.1.1 Epidemiology

There are limited population-based epidemiologic data on achalasia. Most of previous studies were retrospective studies [10]. According to studies conducted in the 2000s, the incidence of achalasia was increasing and does not differ according to ethnicity. The incidence of achalasia was 0.03–0.27 per 100,000 individuals per year in developing countries [11, 12]. In a recent large cohort study using health insurance data in the Netherlands, the incidence of achalasia was 2.2 per 100,000 persons per year [10]. In another study that used tertiary hospital data, the incidence of achalasia was 2.9 per 100,000 persons per year [13]. The prevalence of achalasia is also marginally increasing. A study in the Netherlands reported a prevalence of 15.3 per 100,000 persons per year [10], while in other studies, the prevalence of achalasia was 2.5–32.6 per 100,000

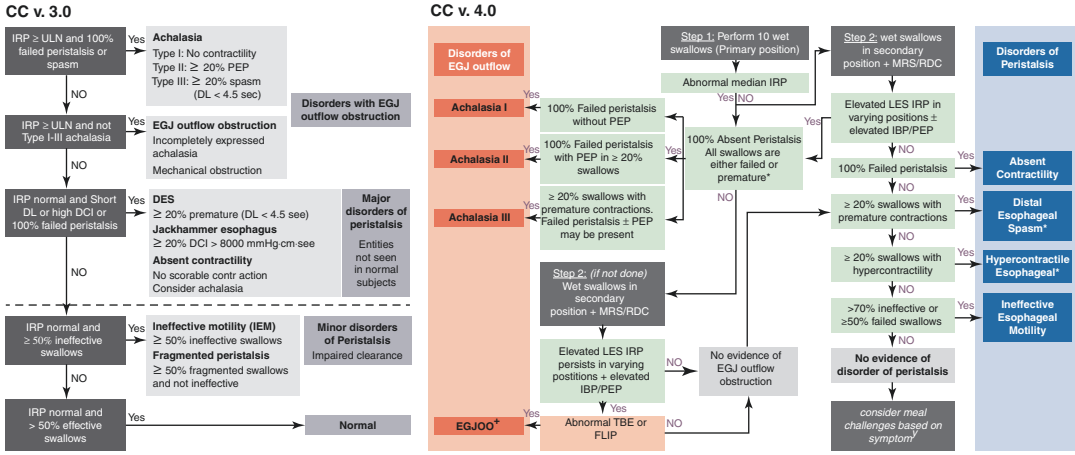


Fig. 5.2 Classification schemes for Chicago Classification version 3.0 and Chicago Classification version 4.0. Key differences in Chicago Classification version 4.0 include the inclusion of supine and upright position and provocative manometric maneuvers (double dagger, yen), the more stringent and refined criteria for esophagogastric junction outflow obstruction (EGJOO) and ineffective esophageal motility (IEM), and as the indication that EGJOO, distal esophageal spasm (DES), and hypercontractile esophagus are manometric patterns of unclear clinical relevance (asterisk). Patients with EGJ obstruction and presence of peristaltic swallows fulfill strict criteria for EGJOO and may have features suggestive of achalasia or other patterns of peristalsis defined by criteria for disorders of peristalsis: EGJOO with spastic features, EGJOO with hypercontractile esophagus, EGJOO with ineffective motility, or EGJOO with no evidence of disordered peristalsis (dagger) (adapted from Yadlapati et al. [8])

persons per year [13, 14]. This increase in the prevalence of achalasia might be attributed to increased use of newer precise medical instruments such as HRM, which has resulted in a decreased rate of misdiagnosis of achalasia as gastroesophageal reflux disease (GERD). However, in a population-based study using a Korean national health database, Kim et al. [15] have reported that the incidence and prevalence of achalasia are 0.4 and 6.3 per 100,000 persons per year, respectively.

5.2.1.2 Cause and Pathophysiology

The pathophysiology of achalasia begins with selective loss of inhibitory ganglion cells in the myenteric plexus of the esophagus, which results in an imbalance of excitatory and inhibitory nerves. This causes an increase in the resting pressure of the LES, insufficient relaxation during swallowing, and loss of normal peristalsis [16]. The cause of the initial decrease in inhibitory neurons in achalasia remains unknown. The initiation of neurodegeneration might be an autoimmune process induced by viral infections (herpes or measles, etc.) in a genetically sensitive host [17]. An inflammatory response is associated with infiltration by T-cell lymphocytes, which results in slow destruction of ganglion cells [9]. The distribution and final outcomes of this plexitis vary. They can be modified by host responses and etiological stimuli [9]. Inflammation of the myenteric plexus can lead to degeneration or dysfunction of inhibitory postganglionic neurons of the distal esophagus, including the LES [18, 19]. These neurons use nitric oxide (NO) and vasoactive intestinal peptide (VIP) as neurotransmitters. Their dysfunction can result in an imbalance between excitatory and inhibitory regulation of the sphincter and adjacent esophagus [20] (Fig. 5.3). Such unopposed cholinergic stimulation can lead to impaired relaxation of the LES, hypercontractility of the lower esophagus, and rapid contraction of the lower esophagus [9].

Most cases of achalasia are of primary or idiopathic causes. In rare cases, achalasia might be secondary to diseases. Such achalasia is called secondary achalasia. One of the main secondary causes is Chagas disease, a parasitic infection caused by *Trypanosoma cruzi*. This disease is

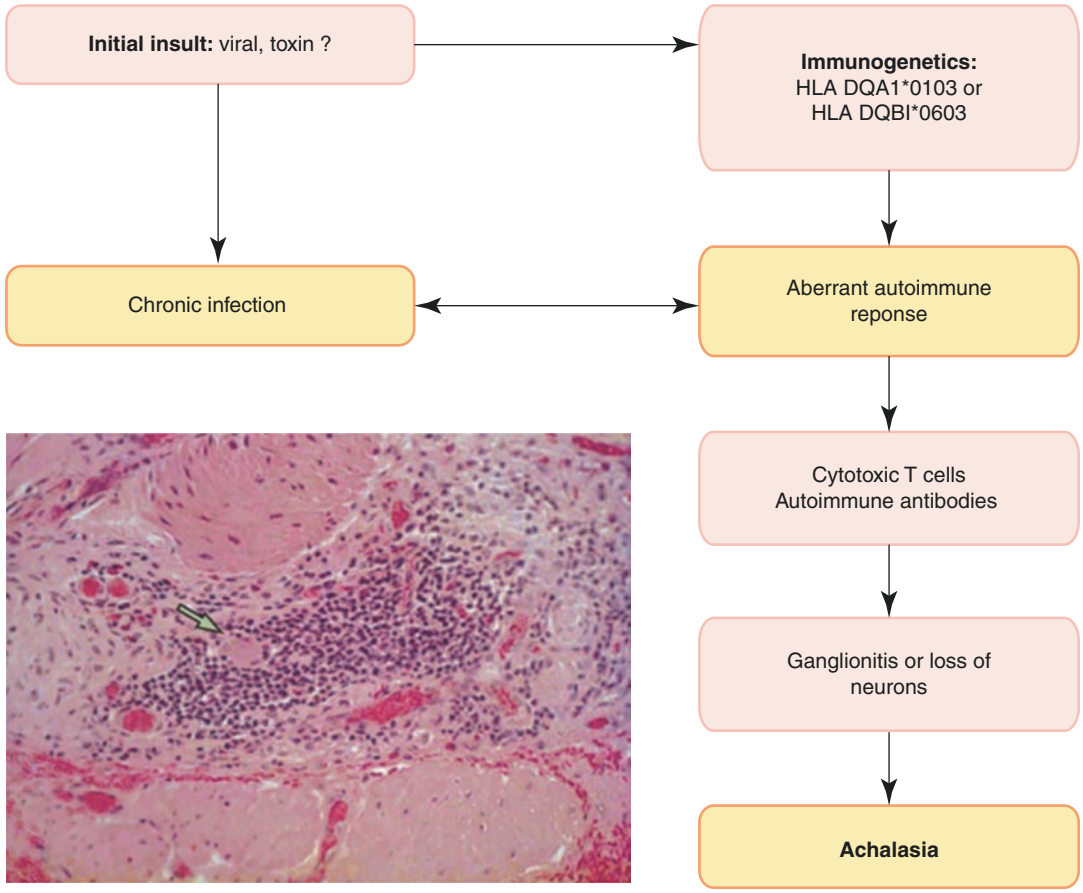


Fig. 5.3 Present hypothesis proposing virus-induced autoimmune-mediated ganglionitis in achalasia. Insert shows infiltration of myenteric ganglion with T-cells. Arrow shows myenteric nerves and ganglion cells (adapted from Boeckxstaens et al. [20])

commonly observed in South American countries such as Brazil. This parasite can invade various organs and induce immune responses over several years. Consequently, the esophageal plexus is damaged, resulting in clinical manifestations similar to those of achalasia [21, 22].

5.2.1.3 Symptoms

Primary symptoms of achalasia include dysphagia, regurgitation, weight loss, chest pain, and heartburn [23–25]. These symptoms are mostly observed in patients aged between 20 and 50 years. The key symptom of achalasia is dysphagia. Cycles of worsening and improvement of dysphagia for solid and liquid foods have been observed, leading to an overall worsening of the condition. Food regurgitation is another common symptom. Regurgitation of undigested food or saliva may be observed at several hours after meals. Symptoms of regurgitation are mainly observed at night. The regurgitated food is characterized by the lack of gastric acid or bile. Additionally, heartburn and chest symptoms have also been commonly reported. These are often mistaken for GERD. The cause of heartburn or chest pain in achalasia is unknown. Some hypotheses for the presence of these symptoms include the following: (1) fermentation of the undigested food retained in the esophagus, which lowers the acidity; (2) ischemia, which temporarily reduces the blood flow to the esophageal mucosa while the circular and longitudinal muscles of the esophagus continue to contract; and (3) pain induced by retention of food in the esophagus. In the past, weight loss was

reported as a common symptom. However, in recent studies, weight loss has not been commonly observed because of increased frequency of intake of high-calorie food.

The Eckardt symptom score is the most commonly used tool to evaluate symptoms of achalasia and the effectiveness of treatment [26, 27]. A score of 0–3 points is given according to the frequency and severity of dysphagia, regurgitation, chest pain, and weight loss. Scores for each symptom are summed to calculate a total score of 0–12 points. In the evaluation of response to treatment, an Eckardt score of less than 3 points indicates a successful treatment [26] (Table 5.1).

5.2.1.4 Diagnosis

5.2.1.4.1 Barium Esophagography

Fluoroscopy can detect barium not passing through the esophagus and repeatedly moving up and down within the esophagus due to non-propulsive tertiary contractions or not moving in the esophagus at all. When a sufficient amount of barium is swallowed by patients, dilation of the esophageal body and impaired relaxation of the LES are observed, showing characteristic findings like a bird's beak. These findings may show different patterns according to three subtypes of achalasia [28] (Fig. 5.4).

Table 5.1 Eckardt symptom score for achalasia (adapted from Eckardt et al. [26])

Score	Dysphagia	Regurgitation	Retrosternal pain	Weight loss (kg)
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5–10
3	Each meal	Each meal	Each meal	>10

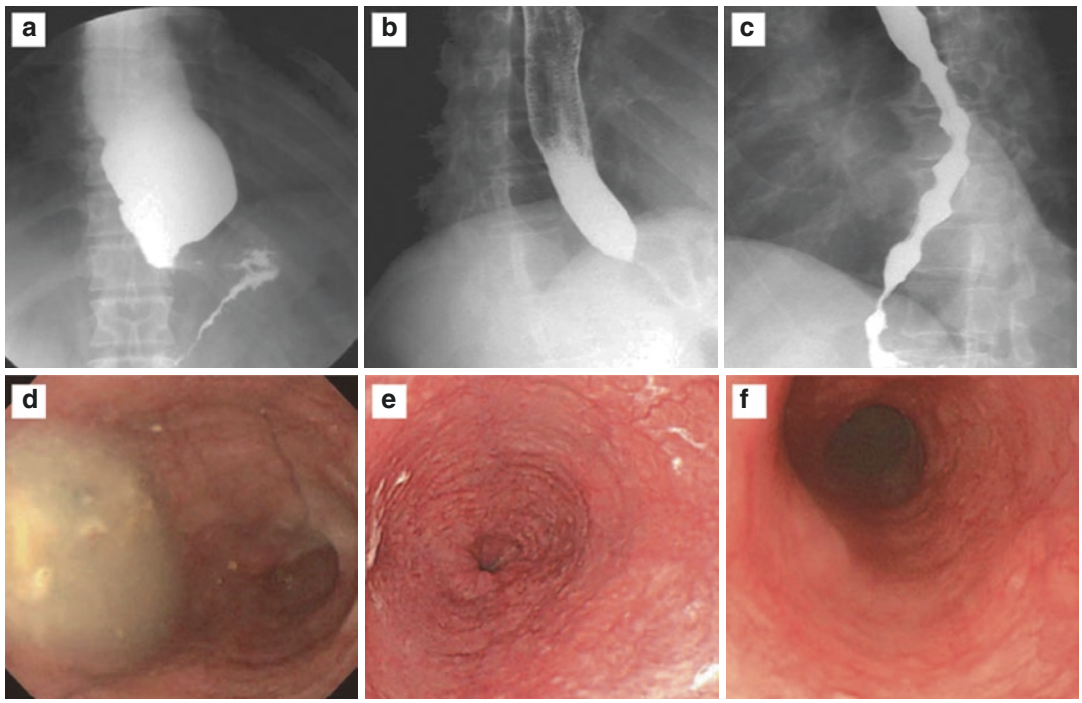


Fig. 5.4 Marked dilatation of the esophagus and bird's beak appearance are noted on the esophagogram (**a**). Moderately dilated esophagus is noted and the proximal esophagus is filled with air on esophagogram (**b**). The associated esophagogram for type III achalasia is often interpreted as esophageal spasm as this has an extreme corkscrew with distal contraction (**c**). Food stasis and flaccid esophagus are noted on the upper gastrointestinal endoscopy (**d**). Narrow gastroesophageal junction is noted on the upper gastrointestinal endoscopy and the scope can pass through with resistance (**e**). Upper gastrointestinal endoscopy findings are nearly normal in type III achalasia (**f**). (adapted from Lee et al. [28])

5.2.1.4.2 Endoscopy

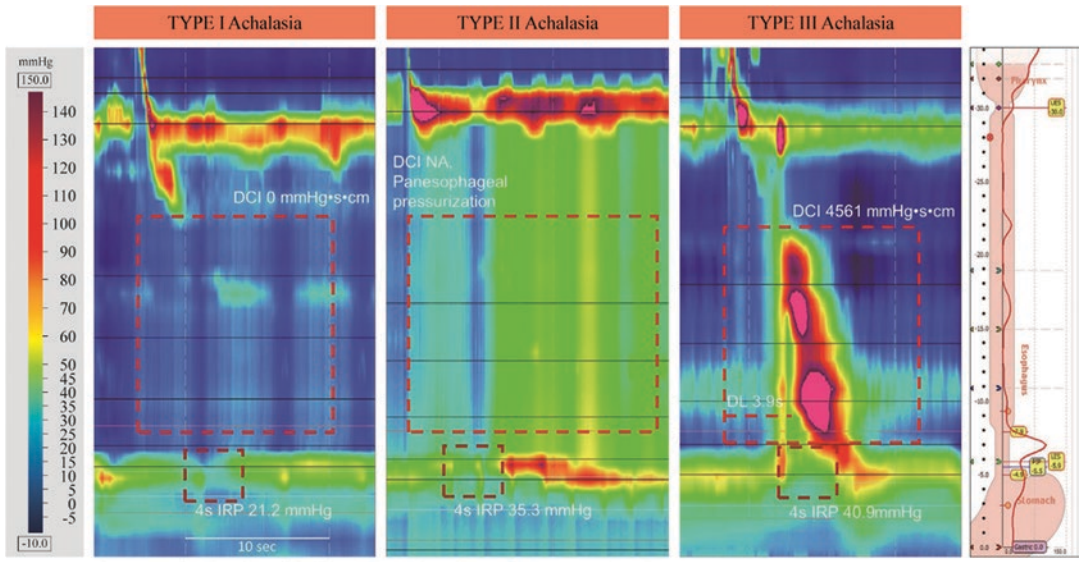
Upper gastrointestinal endoscopy is essential in the evaluation of esophageal mucosa before treatment and to exclude other diseases despite typical findings of achalasia on esophagography, such as relaxed esophageal body, lack of peristalsis, and contracted LES that opens with a slight push with an endoscope. Differences in symptoms might be observed according to the subtype. Typical endoscopic findings include markedly dilated esophageal lumen, lack of effective contractions, and retention of food [28] (Fig. 5.4). In severe cases, a "sigmoid" type of esophagus might be seen with heavy dilation of the esophageal body and rightward curve of the esophagus above the cardiac region.

5.2.1.4.3 Esophageal Manometry

Esophageal manometry is also essential in diagnosing achalasia. Main findings of manometry include a loss of peristalsis of the esophageal body and insufficient relaxation of the LES. These two characteristic findings can confirm the diagnosis of achalasia. Using esophageal pressure topography with HRM, achalasia has been recently classified into three subtypes according to the Chicago Classification [29]: (1) type I with abnormally high integrated relaxation pressure (IRP), which indicates relaxation of the LES without esophageal body motility; (2) type II with a loss of motility of the circular muscle layer and partial motility of the longitudinal muscle layer, which results in panesophageal pressurization in more than 20% of swallowing; and (3) type III with contraction of the lower esophagus in more than 20% of swallowing [6] (Fig. 5.5). In particular, it is known that in type II achalasia, symptom improvement after treatment is significantly higher than that in type II or III achalasia [30, 31]. Additionally, cases with IRP > the upper normal limit with normal esophageal peristalsis are classified as EGJOO or are considered a variant or precursor of achalasia [6].

5.2.1.5 Treatment

Currently, there is no pathophysiology-based treatment for achalasia that can fundamentally restore the loss of esophageal nerve cells and



Courtesy of University of California San Diego Center for Esophageal Diseases

Fig. 5.5 Achalasia subtypes. Type I achalasia: integrated relaxation pressure (IRP) is elevated with failed peristalsis (distal contractile integral, DCI < 100 mmHg-s-cm) without panesophageal pressurization. Type II achalasia: IRP is elevated with failed peristalsis and panesophageal pressurization. Type III achalasia: IRP is elevated with a normal DCI and a reduced distal latency. *NA* not applicable (Adapted from Yadlapati et al. [6])

abnormalities in muscle peristalsis. Prior to the introduction of peroral endoscopic myotomy (POEM), pneumatic balloon dilatation (PD) and laparoscopic Heller myotomy (LHM) were main treatments. These modalities can lower the pressure of the LES, thus inducing the esophageal excretory function and improving symptoms. PD is the most widely used endoscopic therapy with therapeutic effects of 80–90% at 1 year. However, recurrence of symptoms is common, which requires additional treatment in approximately 40–50% of cases within 5 years after the initial treatment. Effects are less sustainable with repetitions of the treatment [32]. LHM can lead to satisfactory outcomes in approximately 64–90% of cases. Partial fundoplication is often performed simultaneously to prevent complications such as gastroesophageal reflux. Although several current treatments are effective with long-term improvements for symptoms, these are more invasive than others. They also require a relatively longer hospital stay. In addition, they are expensive. Moreover, these treatments do not lead to satisfactory outcomes for patients with spastic esophageal diseases that accompany spastic contractions [32].

POEM was first introduced by Inoue et al. [33] in 2010. This endoscopic myotomy involves the natural orifice transluminal endosurgery (NOTES) technique, in which the LES is incised by making a tunnel in the submucosal layer of the esophageal wall through an oral endoscopic approach without a skin incision. Previous studies have demonstrated therapeutic effects and safety of POEM, and in a recent meta-analysis of 36 studies, improvement in symptoms was analyzed for 2373 patients. In approximately 98% of patients (95% confidence interval [CI], 97–100%), Eckardt score improved to ≤3 points with sustained improvements in symptoms for >12 months [34]. Several studies have also reported long-term clinical outcomes of POEM. Improvements in symptoms were sustained for up to 3–5 years in approximately 83–95% of patients, suggesting that POEM could have highly satisfactory mid- to long-term treatment effects [35–38]. Strengths and weaknesses of POEM, LHM, and PD are summarized in Table 5.2 [32].

5.2.2 Distal Esophagus Hypermotility Disorders

Esophageal hypermotility, which leads to increased motility of the esophagus, includes DES, type III achalasia, and hypercontractile (Jackhammer) esophagus [39]. Although these

Table 5.2 Strengths and weaknesses of treatments in achalasia (adapted from Youn et al. [32])

	POEM	LHM	PD
Scarring	No	Yes	No
Selective circular myotomy	Possible	No	No
Concurrent anti-reflux procedure	No	Fundoplication	No
Dissection and disruption of the diaphragmatic hiatus	No	Yes	No
Postoperative incidence of gastroesophageal reflux disease	(+++) 30–40%	(++) 15–20%	(+) 10–20%
Myotomy extension to the proximal esophageal body	Possible	Difficult	Impossible
Hospital stay	Intermediate 3–5 days	Relatively long 5–7 days	Very short 1–2 days
Cost	Intermediate (variable according to region)	High	Low
Clinical response for achalasia	Excellent 95–98%	Good 90–93%	Fair 80–90%
Clinical response for spastic esophageal disorders	Good	Fair	Poor

POEM peroral endoscopic myotomy, *LHM* laparoscopic Heller's myotomy, *PD* pneumatic dilatation

diseases can be differentiated according to findings on HRM, there are no differences in their clinical symptoms or treatment [39].

5.2.2.1 Definition and Pathophysiology

Esophageal motility diseases were collectively termed "diffuse esophageal spasm" in the past. They mainly begin in smooth muscles of the lower esophagus rather than skeletal muscles of the upper esophagus. Therefore, the term "distal esophageal spasm" has been used instead. The pathophysiology of DES and type III achalasia is functional loss of inhibitory ganglionic neurons in the distal esophagus [40, 41]. Disruptions in inhibitory regulation can lead to premature contractions, rapid propagated contractions, and simultaneous contractions of the distal esophagus, which can result in an incomplete relaxation of the distal esophageal sphincter during swallowing. The pathophysiology of hypercontractile (Jackhammer) esophagus is presumed to be cholinergic dominance [42, 43].

5.2.2.2 Clinical Symptoms

Esophageal hypermotility can be observed in all age groups. However, it is most commonly observed in patients between ages of 30 and 40 years and in women. Approximately 30–60% of patients have dysphagia with varying severity day-to-day. Regurgitation symptoms may also be present, however, less common than in achalasia. Chest pain is reported in approximately 80–90% of patients and it is not directly related to dysphagia. The pattern of chest pain is similar to that of angina. Therefore, it must be carefully evaluated. Chest pain is mainly related to diet rather than exercise. It lasts for several hours. It can be relieved by antacids. If symptoms such as heartburn, dysphagia, and regurgitation are also present, then chest pain is highly likely to be caused by esophageal motility disorders. However, ischemic heart disease cannot be rolled out. Additionally, in approximately 20% of patients who complain of chest pain, it is mainly due to hypersensitivity of the esophageal mucosa rather than acid regurgitation. In other cases, various functional gastrointestinal disorders, anxiety disorders, and depression are observed.

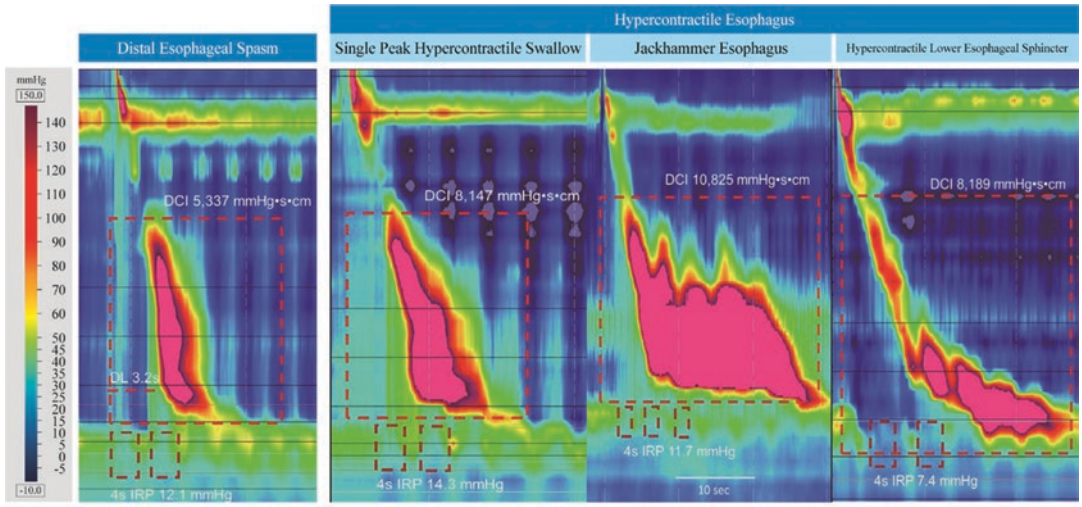
5.2.2.3 Diagnosis

HRM allows for easier diagnosis of esophageal hypermotility using indicators such as distal latency (DL) and distal contractile integral (DCI). The diagnostic criteria in HRM are summarized in Table 5.3 [39, 44] (Fig. 5.6). DES can be diagnosed when at least more than 20% of premature contractions are observed with normal relaxation of the EGJ. DL is used as an indicator of premature contractions. It measures the time between the point of relaxation of the UES and the contractile deceleration point (CDP) at which the contraction slope of the distal esophagus changes. DL < 4.5 s indicates a premature contraction. The only difference between DES and type III achalasia is the relaxation of the EGJ. In type III achalasia, the LES does not relax during swallowing. Jackhammer esophagus can be newly identified using HRM as it can measure DCI, an indicator of continuous contraction pressure of the distal esophagus. Jackhammer esophagus is diagnosed when DCI is >8000 mmHg-cm-s in more than 20% of swallowing. Jackhammer esophagus may be associated with blockage due to EGJOO. It often shows findings of multipeaked contractions. However, this is not an essential criterion for a diagnosis of Jackhammer esophagus [39].

Table 5.3 High-resolution manometry patterns in spastic disorders (adapted from Roman and Kahrilas [39])

Spastic disorder	EGJ relaxation	Esophageal contractions
Distal esophageal spasm	Normal (mean IRP < 15 mmHg)	≥20% premature contractions (DL < 4.5 s)
Type III achalasia	Impaired (mean IRP ≥ 15 mmHg)	≥20% premature contractions (DL < 4.5 s)
Jackhammer esophagus	Normal or impaired	≥20% DCI > 8000 mmHg-s-cm

EGJ esophagogastric junction, *IRP* integrated relaxation pressure, *DL* distal latency, *DCI* distal contractile integral



Courtesy of University of California San Diego Center for Esophageal Diseases; Northwestern Esophageal Center; and Mayo Clinic Arizona Motility Lab

Fig. 5.6 Disorders of peristalsis with esophageal spasticity or hypercontractility. These include distal esophageal spasm (DES) and hypercontractile esophagus. In this example of DES, the DCI is normal with a reduced DL and normal IRP. Hypercontractile esophagus includes sub-groups of single peak hypercontractile swallow, hypercontractile with jackhammer esophagus, and hypercontractile with LES after-contraction. *IRP* integrated relaxation pressure, *DCI* distal contractile integral, *LES* lower esophageal sphincter, *DL* distal latency (adapted from Yadlapati et al. [6])

5.2.3 Differences in Esophageal Motility Disorders Between Sexes

5.2.3.1 Epidemiology of Esophageal Motility Disorders and Differences Between Sexes

In several large-scale epidemiological studies, proportions of male and female patients with achalasia were similar [10, 12, 15, 45]. Achalasia can be observed in all age groups. However, it is most common in patients between ages of 40 and 60 years [10, 12, 46]. DES is a rare disease. Only a limited number of epidemiology studies have assessed it. According to previous studies, the prevalence of symptomatic DES ranges between 3% and 9%. The mean age of prevalence is approximately 60 years. Its prevalence is slightly higher in women at 55% [40, 47, 48]. Jackhammer esophagus is a newer esophageal motility disorder with limited data. In a recent meta-analysis of 38 studies, the prevalence of Jackhammer esophagus was 1.97% [95% CI, 1.39–2.78%] in patients referred to HRM [49]. The mean age at diagnosis was 60.8 years [95% CI, 57.1–64.4] and 65% [95% CI, 58–72%] of patients were women [49].

5.2.3.2 Symptoms of Esophageal Motility Disorders and Differences Between Sexes

A prospective study conducted in Japan included 474 patients with achalasia (248 men and 226 women) who underwent LHM. In that study, female patients with achalasia had a lower body mass index (BMI) ($p < 0.0001$) and less dilation of the esophagus ($p = 0.0061$). The frequency and severity of chest pain before LHM were significantly higher in females than in males ($p = 0.0117$ and $p = 0.0103$, respectively). Improvement in chest pain was also higher in females ($p = 0.0005$ and $p = 0.003$, respectively) [50]. Other prospective studies have reported similar results. In a prospective study that included 213 patients with achalasia (110 men and 103 women) in Iran, chest pain was more common in women than in men (70.9% vs. 54.4%, $p = 0.03$). Furthermore, chest pain decreased in both men and women

after PD or botulinum toxin administration. The decrease was greater in women than that in men (32% vs. 20.9%, $p = 0.04$). In both men and women, chest pain was not related to the symptom duration, LES pressure (LESP), or type of treatment [51]. However, in another study, chest pain was reported to be independent of age and sex [52]. The mechanism of chest pain in achalasia and the reason for its higher frequency in women are not clearly established yet. However, as in GERD, women have more sensitive esophagus, which may lead to higher frequency and intensity of chest pain.

A recent study has analyzed differences in symptoms of achalasia between male and female before POEM and HRM. Dysphagia was more severe in females with achalasia while regurgitation was more severe in males. Heartburn was more frequently observed in males than in female [53]. According to HRM findings, female patients with achalasia had higher LESP and shorter esophageal length than male patients with achalasia. Therefore, the authors believe that this sex differences might be related to the female hormone estrogen. Further analysis was performed by dividing females into pre-menopausal and post-menopausal groups. Results revealed that pre-menopausal females had higher LESP than male and post-menopausal women [53] (Fig. 5.7). Further studies are necessary to assess effects of estrogen on LESP.

5.2.3.3 Response to Treatment Between Sexes

Patients who have demonstrated the greatest benefit with PD are women, those over the age of 40 years, and those with type II achalasia [30, 54–65]. Additionally, patients with type III achalasia, Jackhammer esophagus, and spastic esophageal motility disorders do not show good responses to PD. Among different symptoms of achalasia, only around 50% of patients experience improved chest pain after treatment [26, 44, 66, 67].

Farhoomand et al. [59] have reported that 88% of patients with recurrence of achalasia within 3 months after PD using 3.0-cm balloons are under the age of 45 years and most of them are men. In a study comprising 126 patients, Ghoshal et al. [66] have shown that the male sex, not age, is independently associated with poor outcomes after PD. A large-scale study by the Cleveland Clinic (106 patients with 51 women) has reported that age and sex are equally important variables [63] (Fig. 5.8). It revealed that men under the age of 50 years did not demonstrate good treatment

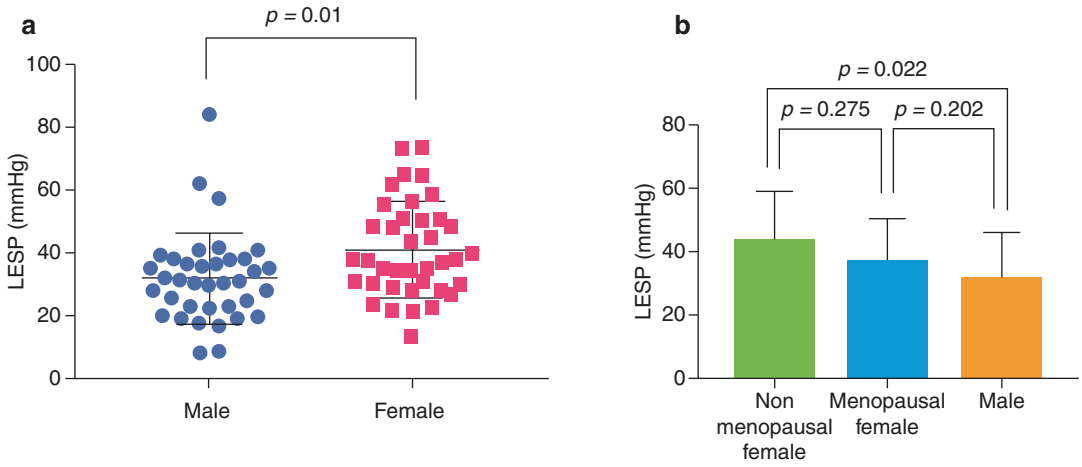


Fig. 5.7 Baseline lower esophageal sphincter pressure (LESP) in patients with achalasia before peroral endoscopic myotomy (POEM). (**a**) Comparison of resting LESP between male and female patients; (**b**) comparison of LESP among non-menopausal female patients, menopausal female patients, and male patients (adapted from Xu et al. [53])

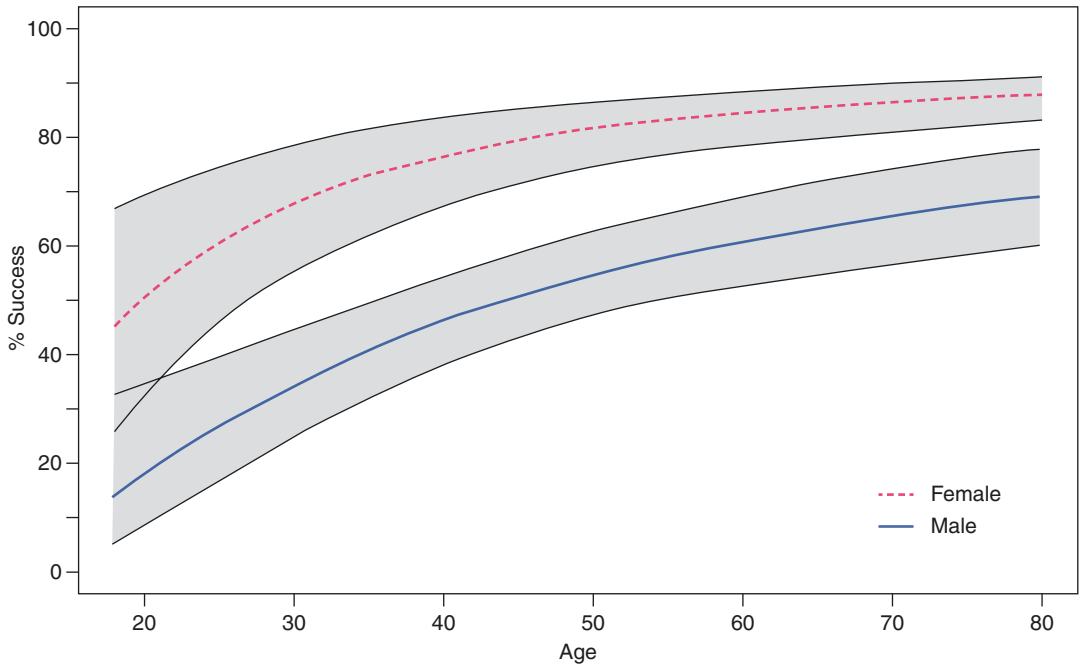


Fig. 5.8 Effect of age and sex on early phase (within 6 months) outcome of single pneumatic balloon dilation (PD), with 95% confidence intervals shown for each curve. Younger patients, especially men, have a higher likelihood of early failure after a single (30 mm) PD. dashed line, women; straight line, men (adapted from Vela et al. [63])

response to a single 3.0-cm PD. However, only young women under the age of 35 years responded poorly to PD, with most women demonstrating satisfactory clinical outcomes for at least 5 years after undergoing a single PD. There might be differences in properties of muscles and tensile strength of the lower esophagus sphincter. However, reasons for such age-related and sex-related differences are unknown [68].

Young patient groups, men, and patients with high LESP have demonstrated good treatment outcomes after primary LHM [63, 69]. A key point is that patients who have no response to PD and Botox can be successfully treated with LHM [63, 70]. However, another study has shown no difference in outcomes of LHM or satisfaction of treatment between sexes [50].

Based on these findings, a suggested treatment algorithm includes LHD for young men and PD for older women [68]. Additionally, Ghoshal et al. [71] have suggested that men should be treated using 3.5-cm balloons as they have poor treatment response to PD. In contrast, they have suggested that women should be treated with 3.0-cm balloons as women demonstrate good treatment response to PD.

There is a lack of studies assessing differences in POEM treatment outcomes between sexes. A recent study has followed up patients who have undergone POEM for more than 6 months and found no differences between sexes in effects of POEM, regurgitation symptoms, HRM findings, or complications of POEM [53].

5.3 Conclusions

Esophageal motility disorders are relatively rare diseases with various symptoms caused by imbalances between excitatory and inhibitory nerves of the esophagus. Representative diseases include achalasia and lower esophageal hypermotility disorders such as DES and Jackhammer esophagus.

There is no difference in the prevalence of achalasia between sexes, although the prevalence of lower esophageal hypermotility disorders is slightly higher in women. The higher frequency of chest pain in female patients with achalasia might be related to esophageal sensitivity. Higher LESP in female patients with achalasia might be attributed to hormones. However, further studies are necessary for detailed assessments and confirmation.

Differences in the response to treatment of esophageal motility disorders between sexes have been reported. Women patients with achalasia responded better to PD than men patients in the past. However, in recent studies, POEM has resulted in better effects and long-term follow-up outcomes, particularly for treatment of distal esophageal hypermotility disorders. Therefore, POEM is increasingly used as the initial treatment of esophageal motility disorders. Future studies must assess differences between sexes in terms of outcomes, complications, and long-term effects of POEM for optimal treatment of men and women with esophageal motility disorders. Based on these studies, treatment of esophageal motility disorders is expected to be tailored for men and women.

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6 Sex Difference of Esophageal Cancer: Esophageal Squamous Cell Carcinoma vs. Esophageal Adenocarcinoma

Nayoung Kim

6.1 Introduction

The effect of sexual disparity on cancer incidence, etiology, and treatment has been relatively overlooked until recently but may be a key component of a precision medicine approach [1]. Large epidemiological studies have demonstrated that sexual differences exist in cancer susceptibility and outcome with males having a higher incidence and poorer outcomes of several tumor types including esophageal cancer (EC) [2, 3]. While some of the differences in cancer incidence may be due to behavioral factors such as smoking and/or hormonal influences [4], it has also been suggested that differential sex-based gene expression signatures [5] and differing immune responses [6] may be important [1]. In addition, the effect of treatment could be different. That is, sexual disparity also affects the pharmacokinetic handling of cytotoxic chemotherapy drugs through differences in body composition [7], drug metabolizing enzyme expression [8], and drug erythrocyte binding [9] with the data suggesting that higher dose intensities may be achieved in females compared to males. This disease ranks seventh in terms of incidence (572,000 new cases) and sixth in mortality overall (509,000 deaths) [2]. Because EC is characterized by rapid growth and early metastasis, most of cases reported have been advanced at diagnosis thus the prognosis is poor [10]. For instance, the 5-year overall survival rate of EC is only 20% in China [10]. Two most common histopathological cell types are esophageal squamous cell carcinoma (ESCC) (Fig. 6.1e and its endoscopic finding Fig. 6.1b) and esophageal adenocarcinoma (EAC) (Fig. 6.1f and its endoscopic finding Fig. 6.1c) in comparison to normal (Fig. 6.1d and its endoscopic finding Fig. 6.1a), and they vary significantly in geographical distribution [11]. Both types of EC are frequent, for instance, 70% in male [10]. In addition, the incidence and mortality are three times higher in male than in female [12] (Figs. 6.2, 6.3). EAC is the more common in Western countries such as the United States (Fig. 6.4a) and Sweden [13] (Fig. 6.4b), and ESCC remains to be the dominant type of EC worldwide, particular in East Asia including China [14], Japan [15], and Taiwan [16] and Korea [17]. The ratio of EAC among esophageal malignancies was as low as 1–4% in Japan [15] and Taiwan [16] and Korea [17]. Furthermore, different histological types of EC have shown different risk factors. An established risk factor for EAC is body fat and that for ESCC is alcohol consumption according

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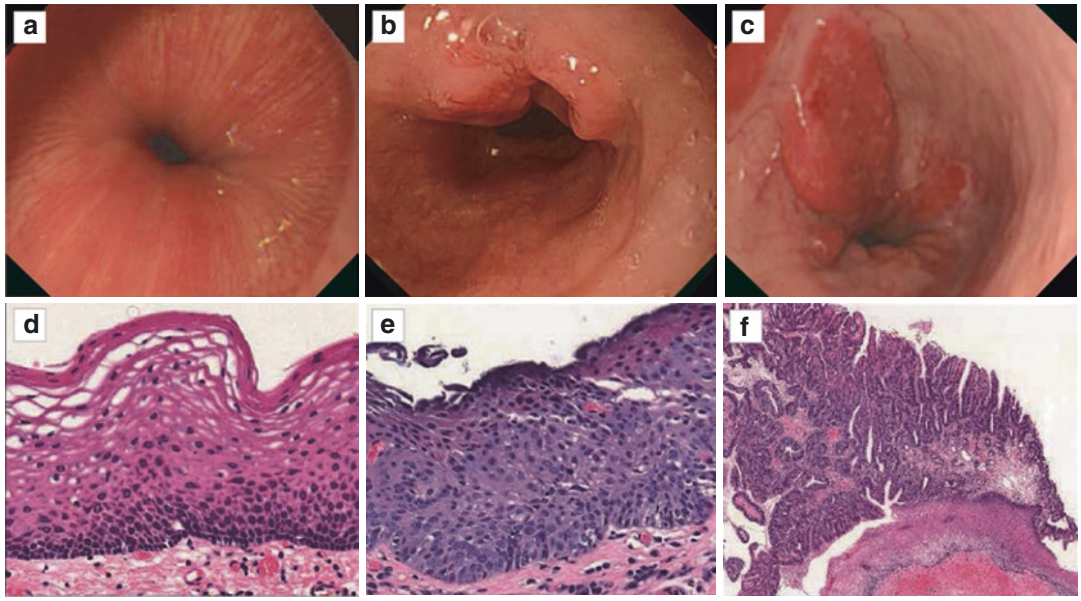

Fig. 6.1 Endoscopic and histological findings of normal (**a**, **d**), esophageal squamous cell carcinoma (**b**, **e**), and esophageal adenocarcinoma (**c**, **f**), respectively

to a systematic review by the World Cancer Research Fund/American Institute for Cancer Research [18]. That is, alcohol intake above 170 g/week significantly increases the risk of ESCC, but not EAC [19]. In case of smoking, it increases risk for both EAC and ESCC [20, 21]. EAC is considered to be an obesity-related disease [21], but the relationship between body mass index (BMI) is mostly limited in Western societies, where overweight or obese population is much higher than in Asian countries [22–24] and where EAC is more common [25, 26]. However, this relationship with BMI in the ESCC is controversial. The striking sex difference (EAC with a male-to-female (M:F) ratio in incidence of up to 9:1 and ESCC 2–3:1) does not seem to be explained by established risk factors, given that the prevalence of the etiological factors and the strengths of associations between these factors and ESCC or EAC risk are similar between the sexes [27]. Sex hormonal factors may play a role in the development of EC, especially EAC; estrogenic exposures may prevent such development, whereas androgens might increase the risk of EAC [27, 28]. In this chapter, epidemiology, pathophysiological characteristics arising from differences in hormonal or other biological parameters, screening, and treatment of EC were reviewed depending on ESCC and EAC.

6.2 Esophageal Squamous Cell Carcinoma

In 2012, EC was the eighth most common form of cancer in incidence and the sixth common cause of death from cancer worldwide, with 456,000 new cases and 400,100 deaths according to the GLOBOCAN 2012 [29]. In 2016, EC became the tenth most common cancer and the sixth leading cause of cancer-related deaths worldwide [30]. In 2018, EC ranks seventh in terms of incidence and sixth in mortality overall, the latter signifying that EC will be responsible for an estimated 1 in every 20 cancer deaths. Its

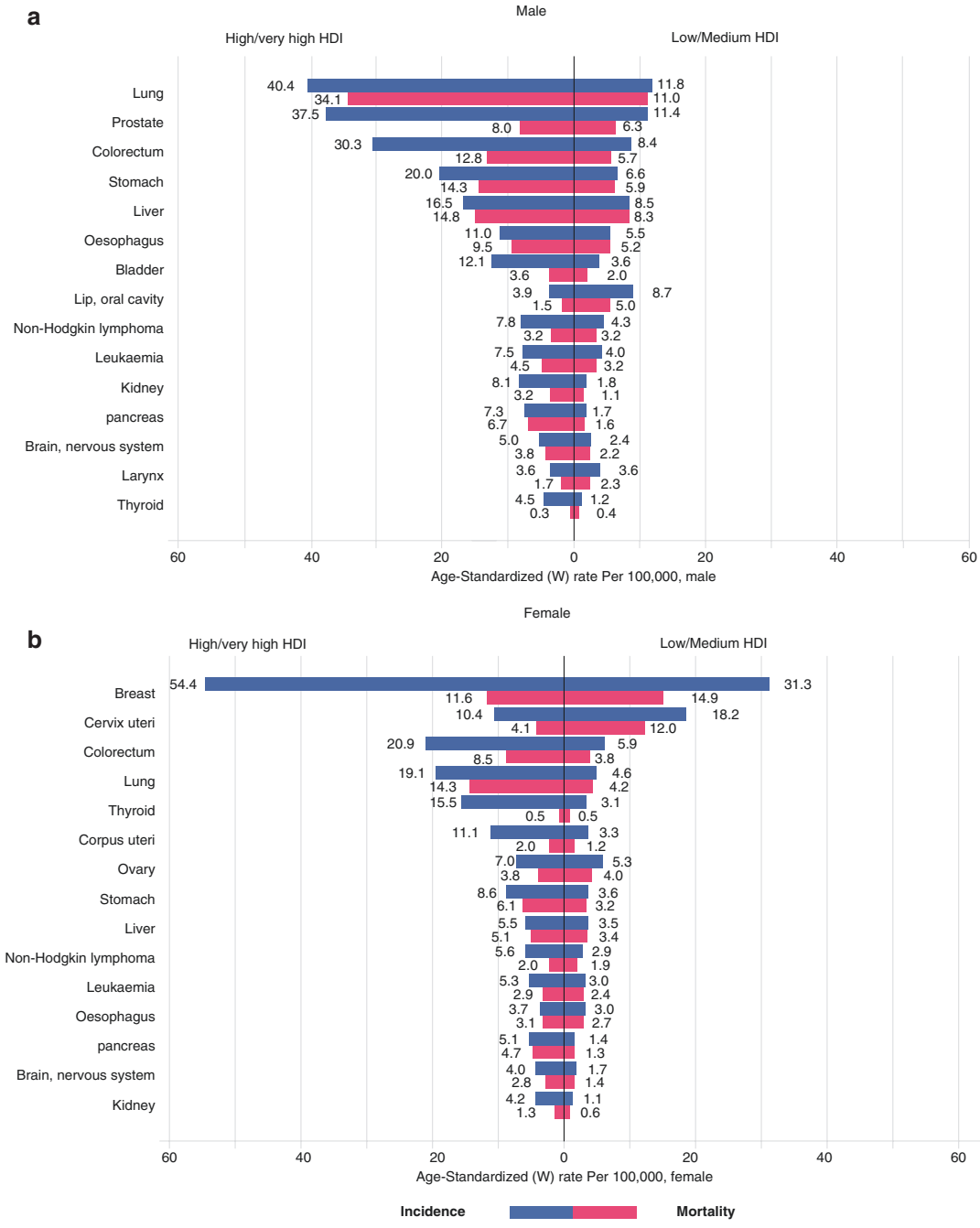

Fig. 6.2 Bar charts of incidence and mortality age-standardized incidence rates in high/very-high human development index (HDI) regions versus low/medium HDI regions among (**a**) male and (**b**) female in 2018. The 15 most common cancers in the world (W) in 2018 are shown in descending order of the overall age-standardized rate for both sexes combined (Source: GLOBOCAN 2018. Adapted from Bray et al. [2])

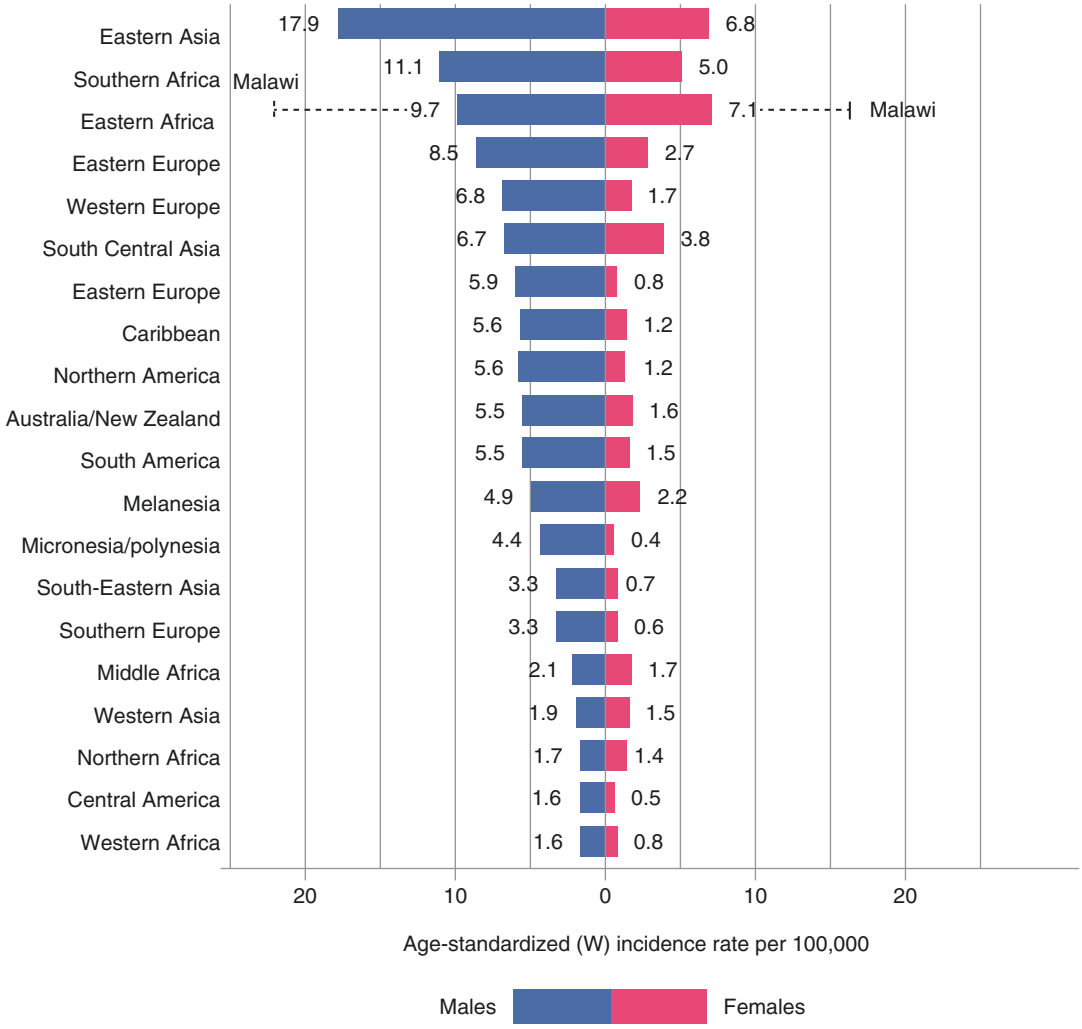

Fig. 6.3 Bar chart of region-specific incidence age-standardized rates by sex for cancers of the esophagus in 2018. Rates are shown in descending order of the world (W) age-standardized rate among men, and the highest national rates among male and female are superimposed (Source: GLOBOCAN 2018. Adapted from Bray et al. [2])

worldwide incidence is believed to be increasing [2]. Age-standardized incidence and mortality rates of EC are the highest in Eastern Asia as well as Southern and Eastern Africa, and around 80% of the cases worldwide occur in less developed regions [29]. Significant disparities exist between sex/genders for the development, progression, and mortality of ESCC, but there is very difference between ESCC and EAC; thus first we introduce the ESCC.

6.2.1 Incidence and Mortality Rate of Esophageal Squamous Cell Carcinoma in the World

The incidence rate of ESCC is highest in Central and South-East Asia, where approximately 80% of all ESCC cases were estimated to have occurred in 2012 [31]. Over half of all new cases of ESCC in the world occur each year in China alone [31, 32]. The incidence of ESCC in male

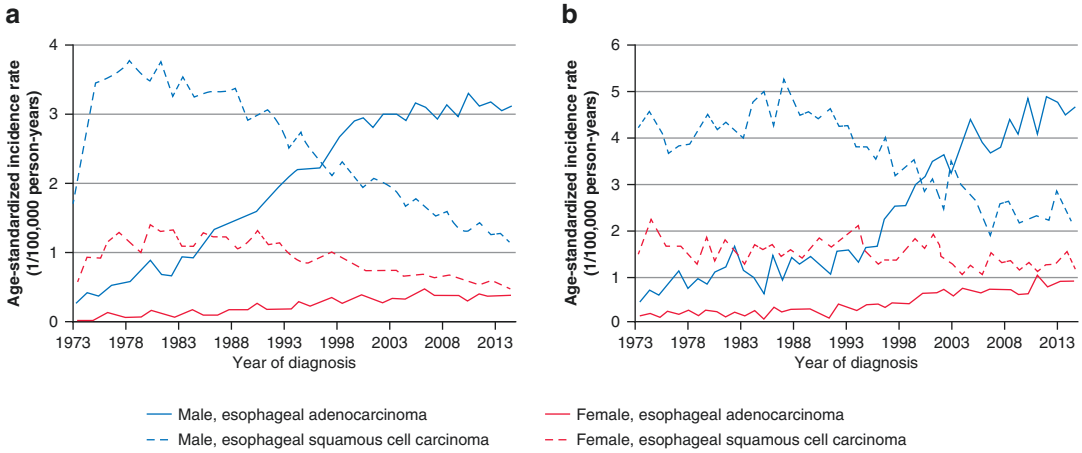

Fig. 6.4 Incidence trends of esophageal squamous cell carcinoma and esophageal adenocarcinoma in the United States (**a**) and in Sweden (**b**). Data sources: the Surveillance, Epidemiology, and End Results (SEER), SEER 9 registries research data, November 2017 submission; and the Swedish Cancer Registry (adapted from Xie et al. [13])

has decreased during the past few decades globally [13]. In female, the incidence has decreased only slightly or stabilized in most regions, but there also appears to be a rise in some countries, including Japan, the Netherlands, New Zealand, Norway, and Switzerland [33]. The incidence of ESCC is substantially higher in rural areas than in urban areas in China and some other Asian populations [34, 35]. In 2011, the incidence of ESCC as well as EAC has shown a male predilection, occurring 3–4 times more commonly in male than female globally [36]. In 2018, approximately 70% of EC cases occur in male, and there was a twofold to threefold difference in incidence and mortality rates between the sexes worldwide (Fig. 6.2) and between regions [2] (Fig. 6.3). Among male, rates are also twofold greater in higher human development index (HDI) countries, with mortality rates ranking fifth in these countries [2] (Fig. 6.2). EC is common in several Eastern and Southern African countries; it was the leading cause of cancer mortality in Kenyan male (Fig. 6.2a), whereas Malawi exhibited the highest incidence rates globally in both male and female [2], suggesting of the difference of environmental factors.

6.2.1.1 Incidence Rate of Esophageal Squamous Cell Carcinoma in Africa

To gain epidemiological insights into ESCC patterns across the African continent, Middletona et al. conducted a systematic review and meta-analysis of male-to-female of EC age-standardized incidence rates (ASR, world) in Africa according to geography, time, and age at diagnosis [37]. These data showed a consistent male excess in incidence rates overall (1.7; 95% CI, 1.4–2.0), and in the high-risk Eastern (1.6; 95% CI, 1.4–1.8) and Southern (1.8; 95% CI, 1.5–2.0) African regions [37]. Within the latter two low risk regions, a male excess was not observed [37]. The high degree of heterogeneity in ESCC incidence implies a large fraction of the disease is preventable and directs research enquiries to elucidate early-age exposures among young male in Africa [37]. Interestingly, in the East African ESCC burden is the unusually high number of young (aged <40 years old) patients [38]. Investigating whether a sex difference is evident in these young age groups, and at what age it manifests, will be valuable in pointing to potential contributions of early life exposures and

inherited susceptibility [37]. The risk factors have not been under active intervention so far and incidence rates of ESCC is increasing consistently in many Eastern and Southern African countries [37]. A male excess of EC was observed for the majority of countries investigated, including the high incidence regions of Eastern and Southern Africa, where a significant male excess predominated [37]. Estimated regional ratios were 1.6 (95% CI, 1.4–1.8) and 1.8 (95% CI, 1.5–2.0) for Eastern and Southern Africa, respectively [37].

6.2.1.2 Incidence Rate of Esophageal Squamous Cell Carcinoma in South Korea

In contrast to Africa, a decrease in incidence of ESCC has been observed in both developing and developed countries [39, 40]. Similarly, the incidence of ESCC has decreased in Korea for the past 15 years [39] (Fig. 6.5), where histological type of EC is ESCC type (90.2%) in 2013 which is very similar to Africa [39]. This EC incidence data during 1999 to 2013 came from the Korea Central Cancer Registry, covering the entire population reported [39]. The ASR decreased from 8.8 per 100,000 populations in 1999 to 5.9 in 2013 with an annual percent change of 2.6% in male and 2.2% in female [39] (Fig. 6.5). The same decreasing trends were observed for both male and female with annual percent changes (APCs) in the incidence rates of EC 2.6% and 2.2%, respectively [39] (Fig. 6.5b, c). More than 90% of all EC cases were male and the most frequent was ESCC, constituting 75.5% of all cases in 1999, gradually increasing to 90.2% in 2013 but after excluding unspecified histology cases, the proportion of ESCC was 92.5% in 1999 and 96% in 2013 [39]. In male, the ASRs of all histological types significantly decreased, whereas in female, the ASR of unspecified EC decreased, but that of EC did not change between 1999 and 2013 [39].

6.2.1.3 Mortality Rate of Esophageal Squamous Cell Carcinoma in South Korea

A decrease in mortality of ESCC has been observed in both developing and developed countries [39, 40]. In Korea 5-year relative survival of ESCC improved from 12.1% (1993–1995) to 34.6% (2009–2013) [39]. This significant improvement of 5-year survival rates may be attributable to more effective detection of early-stage disease with the increased proportion of localized and regional cancer compared with that of distant cancer [39]. This is originated from the strategy of the Korean government. Endoscopy

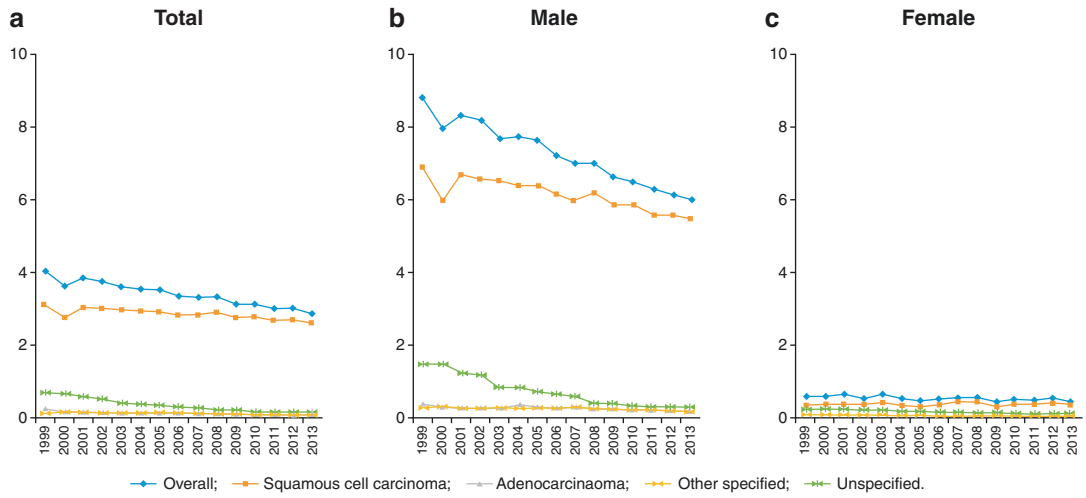

Fig. 6.5 Age-standardized incidence rates of esophageal cancer in (**a**) total (**b**) male and (**c**) female in South Korea (adapted from Shin et al. [39])

or upper gastrointestinal series has been covered from the age from 40 years old biannually for the early detection of gastric cancer by the Korean government, which has been implemented in 2002 as a part of the National Cancer Screening Program (NCSP). Trends of EC according to Surveillance, Epidemiology, and End Results (SEER) staging shows that the proportion of patients diagnosed as localized stage increased from 30.1% in 2006–2009 to 33% in 2010–2013 and that of regional stage increased to 37.8% from 32.7%, respectively [39]. Consequently, overall relative survival rate (RSR) markedly improved during the observation period. Overall 5-year RSRs were 12.8% between 1993 and 1995 but increased to 33.4% between 2009 and 2013 [39] (Fig. 6.6). In terms of the tissue type of EC, there was a slight difference. That is, between 1993 and 1995, the 5-RSRs for ESCC and EAC were 12.1% and 15.7%, respectively, but between 2009 and 2013, the former was 34.6% and the latter was 29.6% [39]. When comparing the RSRs by sex, there was a remarkable improvement in RSR of male with ESCC [39] (Fig. 6.6). Improvements in RSR were observed in localized and regional cancer patients diagnosed in 2009–2013 compared with patients diagnosed in 2006–2008 [39] (Fig. 6.6). Particularly, the 5-year survival rate of localized cancer was 49.5% during 2006–2008, and it improved significantly to 58.5% between 2009 and 2013 [39] (Fig. 6.6). Relative excess rates (RER) was 0.72 (95% CI, 0.65–0.80) in localized cancer and 0.88 (95% CI, 0.82–0.95) in regional cancer among patients diagnosed in 2009–2013, compared with those in 2006–2008 [39] (Fig. 6.6). Taken together sex RER was most reduced in male with localized stage [39].

6.2.2 Pathophysiology of Esophageal Squamous Cell Carcinoma

Lower socioeconomic status, as indicated by lower income or education, has consistently been associated with an increased risk of ESCC in studies from both developing and developed

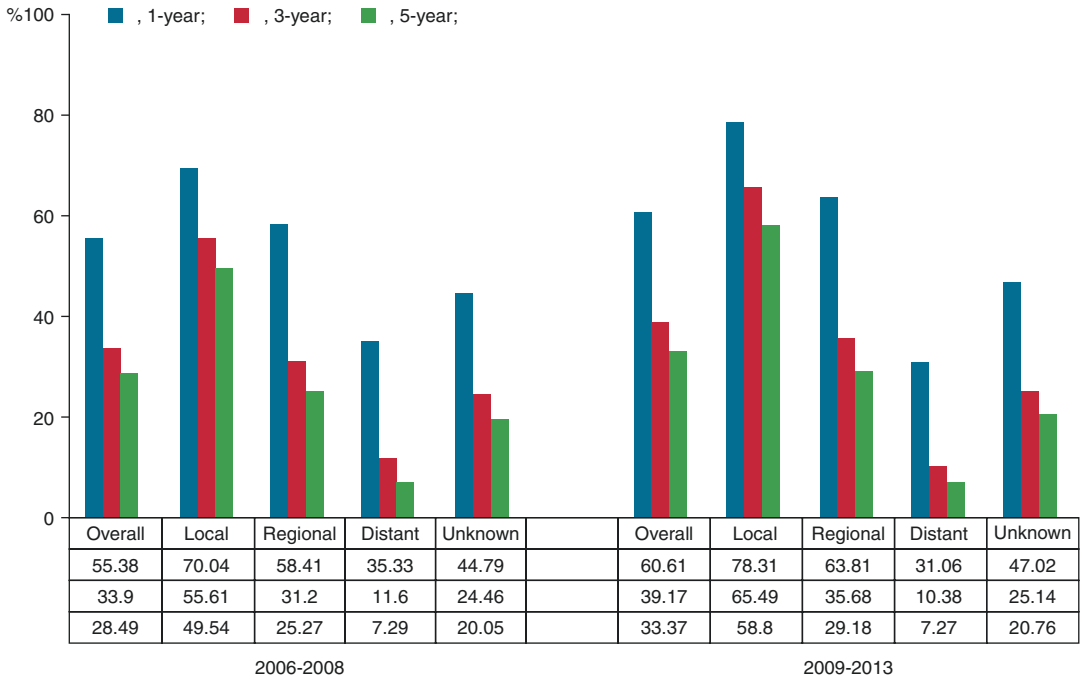

Fig. 6.6 Relative survival rates (%) of 1, 3, and 5 years of patients with esophageal cancer by period of diagnosis according to Surveillance, Epidemiology, and End Results stage (adapted from Shin et al. [39])

countries [32, 35]. A nationwide case-control study in Sweden also found an approximately fourfold increased risk of ESCC in skilled manual workers compared with professionals, after adjustment for tobacco smoking and alcohol use [41]. Differences in socioeconomic status may contribute to the rural-urban disparity in the incidence of ESCC. Heavy drinking and smoking and their synergistic effects are the major risk factors for ESCC [42]. However, in lower-income countries, such as in parts of Asia and sub-Saharan Africa, the major risk factors for ESCC (which usually comprises over 90% of all EC cases) have yet to be elucidated [2]. In addition, the high-incidence countries in Eastern and Southern Africa have yet to be elucidated, and research is needed to address the role of these factors and other dietary components (e.g., nutritional deficiencies, nitrosamines) [43]. However, it is evident that several potential contributors, e.g., tobacco and alcohol use, are more prevalent among males [44] and fundamentally there is sex hormone difference.

6.2.2.1 Sex Hormone

As ESCC prevalence is higher in male than in female, androgen received more attention than estrogen. In 1985, Kobayashi [45] investigated the effects of sex hormones on the development of ESCC in a rat model. The highest incidence of ESCC was in male rats, followed by female rats treated with testosterone. This fell to 0% in castrated rats treated with estradiol [45]. Female rats with no hormonal manipulation also had low rates (8%) [45]. The authors concluded that ESCC growth is inhibited by estrogen and stimulated by androgens. However, the expression of ARs was not addressed in this study. Matsuoka et al. [46] were the first to detect ARs in a cell line (KSE-1) derived from a male ESCC. The KSE-1 cell line had a binding content of 4.2 fmol/mg protein for the ER and 2.2 fmol/mg of protein for the AR in the cytoplasm [46]. Proliferation of this cell line was suppressed by estrogen and accelerated by testosterone. Ueo et al. [47] characterized ARs and conducted treatment experiments in two ESCC cell lines, KSE-1 and KSE-2. Similar to Matsuoka et al. [46], the proliferation of KSE-1 was increased by dihydrotestosterone (DHT) and decreased by estradiol, although sex hormones had no impact on the growth of KSE-2. Receptor analysis found KSE-1 to be positive for both AR and ER, but KSE-2 was negative for both. In a mouse xenograft model, KSE-1 tumor growth was suppressed by estradiol, whereas no effect was seen in KSE-2. Interestingly, no growth-promoting effect was seen with DHT in either cell line in vivo, which is consistent with the concept of testosterone saturation in the context of prostate cancer [48]. Tanaka et al. [49] further investigated KSE-1 and found that the tumor growth stimulation that occurs with AR activation is mediated by fibroblast growth factor 8 (FGF-8) signaling known as androgen-induced growth factor. Furthermore, Yamashita et al. [50] identified ARs in ESCC specimens from 21 patients. Two tumors were successfully xenografted into male nude mice and cultured as cell lines, and the growth of the cell lines in the presence of sex hormones was assessed. Similar to the other studies, testosterone stimulated growth, whereas estrogen had no impact [50]. Tihan et al. [51] used immunohistochemistry to determine AR expression in ESCC resection specimens. Positive staining for AR was found in 3 of 14 (21%) specimens [51]. No differences in survival were found with respect to AR status, but the study size was small [51]. Yang et al. [52] detected ARs and ERs in ESCC specimens from 31 patients (26 male, 5 female) using a radio-ligand binding assay method. Compared with the normal esophageal tissues, more ARs were detected in the ESCC tissues (40.56 ± 18.19 vs. 7.84 ± 3.21 fmol/mg) [52]. The expression of AR correlated with sex, tumor differentiation, invasion, and the lymph node metastasis status, but not age of the patient or tumor location [52]. The authors concluded that the expression of AR impacts on the biological behavior and prognosis of ESCC [51, 52]. Dietzsch et al. [53] investigated androgen pathways in ESCC arising in South African males by targeting AR mutations which were known to occur in prostate cancer. As in prostate cancer, known AR mutations were associated with increased susceptibility to the disease [53]. It suggested that the mutation in

question (a short (GGC)n allele) increases AR activity, which would explain the increased incidence of this cancer in male with this mutation, and also suggested the implication of AR signaling in the pathogenesis of the disease, at least in some patient populations [53].

6.2.2.2 Alcohol

Alcohol consumption is one of the most important known risk factors for human cancers, and there is convincing evidence that alcohol consumption increases the risk of cancer in the colorectum, female breast, larynx, liver, esophagus, oral cavity, and pharynx [10]. Ethanol from alcoholic beverages is metabolized to acetaldehyde, which was classified as a human carcinogen by the IAARC. Ethanol itself can cause local irritation of the upper GI tract and could stimulate carcinogenesis by DNA methylation. Excess use of alcoholic beverages has been consistently associated with an increased risk of ESCC [13]. The association seems to be stronger in lower-incidence Western countries than in higher-incidence Asian countries [32]. Studies from the United States have shown that overconsumption of alcohol is associated with an as high as ninefold increased risk of ESCC and may explain over 70% of all ESCC cases [54, 55]. Studies from Asian populations have reported relative risks of ESCC ranging from 1.6 to 5.3 associated with alcohol consumption [32]. This wide variation in relative risk estimates may be explained by differences in exposure patterns, vulnerability of the study populations, study design, and ability to adjust for confounders [34, 35]. In terms of joint effects of low BMI and alcohol consumption on developing ESCC, our team performed a Korean nationwide population-based cohort study from a total of 264,084 individuals aged 40 years or older, who received healthcare check-ups arranged by the national insurance program, between 2003 and 2008 [10]. There were newly diagnosed 278 EC during a median follow-up duration of 7.9 years [10]. Alcohol consumption increased risk for EC in a dose-dependent manner and those who consumed alcohol daily showed a 2.8-fold increase in the risk of EC compared with never drinkers [10]. Heavy alcohol consumption in individuals with underweight increased the risk of developing EC dramatically, suggesting underweight was a risk factor for ESCC. Thus achieving normal range of BMI is important to reduce the risk of ESCC, especially in case of alcoholics [10].

6.2.2.3 Smoking

Tobacco smoking is a major risk factor for ESCC in both developed and developing countries, although the association seems to be stronger in developed populations. A recent meta-analysis of 52 studies revealed an approximately fivefold increased risk of ESCC in current smokers compared with non-smokers in Western countries and a corresponding threefold increased risk in Asia and South America [56]. Over half of all ESCC cases have been estimated to be attributable to tobacco smoking in the United States [54, 57]. The use of tobacco products other than cigarettes may increase the risk of ESCC with a seemingly similar magnitude of association as cigarette use, but more accurate population-specific estimates are warranted before these findings can be established [32]. Compared to individuals who continue tobacco smoking, those who stop smoking have a gradually decreased risk of ESCC over time, and this effect is more pronounced in Western than in Eastern populations [56]. A recent meta-analysis of 41 studies reported a 66% decreased risk of ESCC in individuals who had quit smoking over 20 years ago (odds ratio [OR] 0.34; 95% CI, 0.25–0.47), compared with current smokers [56].

6.2.2.4 Dietary Factors

A large number of studies from all over the world have investigated associations between various dietary factors and ESCC risk. However, existing evidence remains limited to associate ESCC risk with any specific nutrients or food items [13]. This is due to the complexity of dietary assessment, particularly inter-correlations between individual items, and confounding from other risk factors, e.g., tobacco smoking, alcohol use, and socioeconomic status [13]. Numerous studies have reported increased risk of ESCC associated with high intake of pickled vegetables and low intake

of fresh fruit and vegetables [32, 58, 59], but evidence from high-quality prospective studies remains largely lacking. The International Agency for Research on Cancer (IARC) has concluded that the evidence from humans is "limited" regarding the carcinogenicity of pickled vegetables and the evidence from experimental animals was "inadequate" [60]. The World Cancer Research Fund Continuous Update Project for the esophagus recently concluded that evidence regarding intake of fruit and vegetables and a decreased risk of ESCC is also "limited" [18]. A large randomized intervention trial with 26 years of follow-up in a nutrient-deficient population in China found no benefit of multivitamins supplementation in reducing EC-specific mortality [61]. Consumption of hot food and beverages has been investigated in relation to ESCC risk in over 60 studies [62]. The most recent meta-analysis showed a twofold increased risk of ESCC associated with consumption of hot food or drinks, and the pooled odds ratios were stronger in developing countries (2.80; 95% CI, 2.05–4.02) than in developed countries (1.65; 95% CI, 1.17–2.33) [63]. However, most available studies on this topic have had methodological limitations, i.e., inaccurate exposure assessment, insufficient adjustment for confounders, or recall bias. IARC recently concluded that evidence in humans for carcinogenicity of drinking very hot beverages was "limited" [64]. A recent population-based cohort study of over 450,000 participants in China suggested an increased ESCC risk associated with hot tea consumption, particularly when combined with excess alcohol use and tobacco smoking [65]. Yet, the causality of consumption of hot foods and beverages in relation to the risk of ESCC remains to be confirmed in more large and well-designed prospective studies.

6.2.2.5 Lower Body Mass Index

While most studies have evaluated the association between overweight or obesity and cancer, the impact of underweight on cancer susceptibility has been relatively ignored. In terms with EC, researchers have evaluated mostly smoking tobacco, alcohol drinking, and poor diet (low fresh fruit and vegetable intake) as risk factors for EC rather than BMI. One report showed the evidence for low BMI or leanness as a factor associated with an increased risk of ESCC in Western and Asian populations [66]. In addition, our analysis showed that individuals with a BMI of less than 18.5 kg/m^2 had a 73% increase in the risk of developing ESCC compared with normal-weight subjects (BMI 18.5–22.9 kg/m^2), while individuals with a BMI of greater than 25 kg/m^2 had a 30% decrease in the risk of developing EC [10]. Poor diet leading to micronutrient deficiencies or malnutrition reflected in low BMI has been implicated as one of the underlying mechanisms explaining higher risk of ESCC [67, 68]. Low BMI can be a good indicator of long-term malnutrition, but specific micronutrients, which may affect the development of EC, need to be discovered. While other studies on the inverse association between BMI and ESCC risk have paid attention to the possible confounding effects of smoking [66, 69–71], our team stratified the amount of alcohol consumption to assess its possible impact on increased risk of ESCC and found the synergistic effect of heavy drinking and underweight on the vulnerability of EC [10]. The carcinogenicity of alcoholic beverages in relation to ESCC may most likely be due to both ethanol itself and acetaldehyde, which is a carcinogen derived from ethanol metabolism [72]. The effects of this may further be amplified by undernutrition, which is usually associated with insufficiency of micronutrients from improper maintenance of antioxidants and immune functions [73–75]. There is evidence of protective effects from diets that are rich in fruits, vegetables, and whole-grain cereals on both ESCC and EAC [59, 76, 77]. When the preventive effect of weight gain on development of EC was evaluated by categorizing subjects according to change of BMI between baseline and at 2- and 4-year health check-up, weight loss was associated with developing of ESCC and weight gain was associated with reduced risk of ESCC [10]. This finding that BMI is inversely associated with the risk of EC—mostly ESCC—when restricted to non-smokers is in accordance with the results from two large studies [66–68, 70]. Although current smoking status did not significantly contribute to the

inverse relationship between underweight and EC development, there was a higher prevalence of EC among those with lower BMI among smokers [10].

6.2.2.6 Genetics

There are conditions with a genetic basis, such as Tylosis, an autosomal dominant disease, that are clearly related to the development of ESCC. Familial aggregation in population of high incidence of EC, such as northern regions of China, has also been reported [78]. Four genome-wide association studies (GWAS), three of them conducted in Chinese population and one in Japanese population, have shown genetic susceptibility factors in the development of ESCC, especially in heavy alcohol and tobacco users. Two nucleotide polymorphisms (SNPs, single-nucleotide polymorphisms) deserve special attention because they encode enzymes metabolizing alcohol: alcohol dehydrogenase 1B (rs1229984, OR 1.79) and aldehyde dehydrogenase 2 family (rs671, OR 1.67) [79]. Other GWAS found association at two loci, one located in the enzyme phospholipase C and another in a particular region of chromosome 20 (C20orf54) [80]. Regarding association with ESCC, a GWAS dataset that included 453,852 SNPs from 1898 ESCC patients and 2100 control subjects of Chinese population was reviewed [81]. The authors identified candidate causal SNPs, and pathway (ICSNPathway) analysis identified seven candidate SNPs, five genes, and seven pathways, which together revealed seven hypothetical biological mechanisms [81]. The three strongest hypothetical biological mechanisms were rs4135113, rs1800450, and rs3769823 [81].

6.3 Esophageal Adenocarcinoma

The incidence of EAC has increased rapidly during the past four decades in many Western populations, including North America and Europe [27]. The established etiological factors for EAC include gastroesophageal reflux disease (GERD) with Barrett's esophagus (BE) and obesity, *H. pylori* infection, tobacco smoking, and consumption of fruit and vegetables. Strangely there is a marked male predominance of EAC with a male (M):female (F) incidence ratio in incidence of up to 9:1. The striking sex difference does not seem to be explained by established risk factors, given that the prevalence of the etiological factors and the strengths of associations between these factors and EAC risk are similar between the sexes [27]. Instead sex hormonal factors may play a role in the development of EAC; estrogenic exposures may prevent such development, whereas androgens might increase the risk of EAC [28]. However, continuing research efforts are still needed to fully understand the reasons for the male predominance of EAC.

6.3.1 Incidence and Mortality Rate of Esophageal Adenocarcinoma in the World

The past four decades have witnessed a markedly increasing incidence of EAC in Western regions, including Europe, Northern America, and Australia, and the incidence of EAC has surpassed that of ESCC in many Western countries [82–84]. The incidence of EAC is substantially higher in whites than in other races in the United States [85]. EAC has a striking male predominance in incidence, with a M:F incidence ratio of 6-to-1 in general and as high as 8-to-1 in some populations, e.g., in the Unites States [27, 83] (Fig. 6.4a). In addition, M:F ratios are ranging from 5:1 in France, 6:1 in Australia and Sweden, and 10:1 in the United Kingdom [86–88]. The geographic distribution of EAC shows that among 52,000 new cases of EAC (41,000 in male and 11,000 in female) worldwide in 2012, a total of 12,000 (22.8%) occurred in Europe and 11,100 (21.2%) in North America [31]. In addition, an analysis of the SEER Registry in the United States confirmed a significant rise in EAC among males and a slower rise in females from 1973 to 2008, with an overall M:F ratio of 7.66 [88].

Mathieu et al. [88] analyzed the EC incidence trends by histology and sex from 1973 to 2008 in nine population-based cancer registries of SEER 9 Registry Database in the United States. When

they used age as a proxy for estrogen exposure in females, the collective age groups annual percentage change in EAC for females was positive (0.03%, 95% CI, 0.02–0.03%) during the study period [88] (Fig. 6.7a). Interestingly, the EAC annual percentage change in incidence rates for females during the same time period was significantly negative from ages 50–54 to ages 60–64 [88] (Fig. 6.7b). Even though the incidence of EAC rises in both males and females, the male-to-female ratio across age peaks in the 50–54 years then decreased [88] (Fig. 6.7c). Furthermore, the EAC age-adjusted incidence rate in post-menopausal females age 80 and above increased with age unlike their male counterparts [88] (Fig. 6.7c). Taken together, these data support the hypothesis that the endocrine milieu in pre- and peri-menopausal females serves as a protective factor against EAC, and with loss of estrogen or due to the increasing time period away from estrogen exposure, the rate of EAC incidence increases in the older post-menopausal female.

The prognosis in patients with EAC is worse than that for most other types of tumors, with the overall 5-year survival lower than 15% [27]. A noteworthy sex difference in prognosis among patients with EC has been consistently shown. Female patients have longer survival than male patents, which might be explained by the differences in extrinsic risk factors for mortality or possibly sex itself [89–91]. However, the sex difference in survival was apparent only in ESCC instead of EAC in a large register-based study in the United States [89]. A large pooled analysis using prospective randomized trial data showed sex difference in the treatment and prognosis [1]; 3265 patients were included for survival analysis (2668 [82%] male, 597 [18%] female; 2627 (80%) < 70 years, 638 (20%) > 70 years) [1]. A significant improvement in overall survival (OS) (HR 0.78; $p < 0.001$) and disease-specific survival (DSS) (HR 0.78; $p < 0.001$) was observed in females compared with males. However, no significant differences in OS (HR 1.11; $p < 0.045$) or DSS (HR 1.01; $p < 0.821$) were observed in older patients compared with younger patients [1]. For patients who underwent resection, older patients (15% vs. 10%; $p < 0.03$) and female patients (14% vs. 10%, $p < 0.10$) were more likely to achieve favorable Mandard TRG scores [1]. The role of sex itself in the prognosis of EAC still needs to be verified in further independent studies, considering the lack of information on important possible confounders in previous studies.

6.3.2 Pathophysiology of Esophageal Adenocarcinoma

EAC represents the majority of EC cases in high-income countries, with excess body weight and GERD among the key risk factors [42]. The established etiological factors for EAC include gastroesophageal reflux-related BE and obesity, decrease of *H. pylori* infection, tobacco smoking, and consumption of fruit and vegetables. A marked male predominance of EAC with a M:F ratio in incidence of up to 9:1 may be partly explained by both extrinsic and intrinsic exposures that are differentially distributed between the sexes or more harmful in male than in female. However, this sex difference does not seem to be explained by established risk factors alone, given that the prevalence of the etiological factors and the strengths of associations between these factors and EAC risk are similar between the sexes. Recent molecular evidence suggests hormonal factors. That is, the preventive effect of estrogen and provoking mechanism of androgens are helpful to explain this sex difference of EAC.

6.3.2.1 Sex Hormone

The male predominance in EAC may be caused by a delayed development of, on average, 16 years in female compared with male [92], suggesting a protective role of sex hormones and reproductive factors in the development of EAC. The hypothesis of sex hormonal influence in the etiology of EAC has been tested in patients diagnosed with sex hormone-related cancers, namely, breast and prostate cancers. If sex hormones play a role in the development of EAC, an altered risk of EAC might be evident among

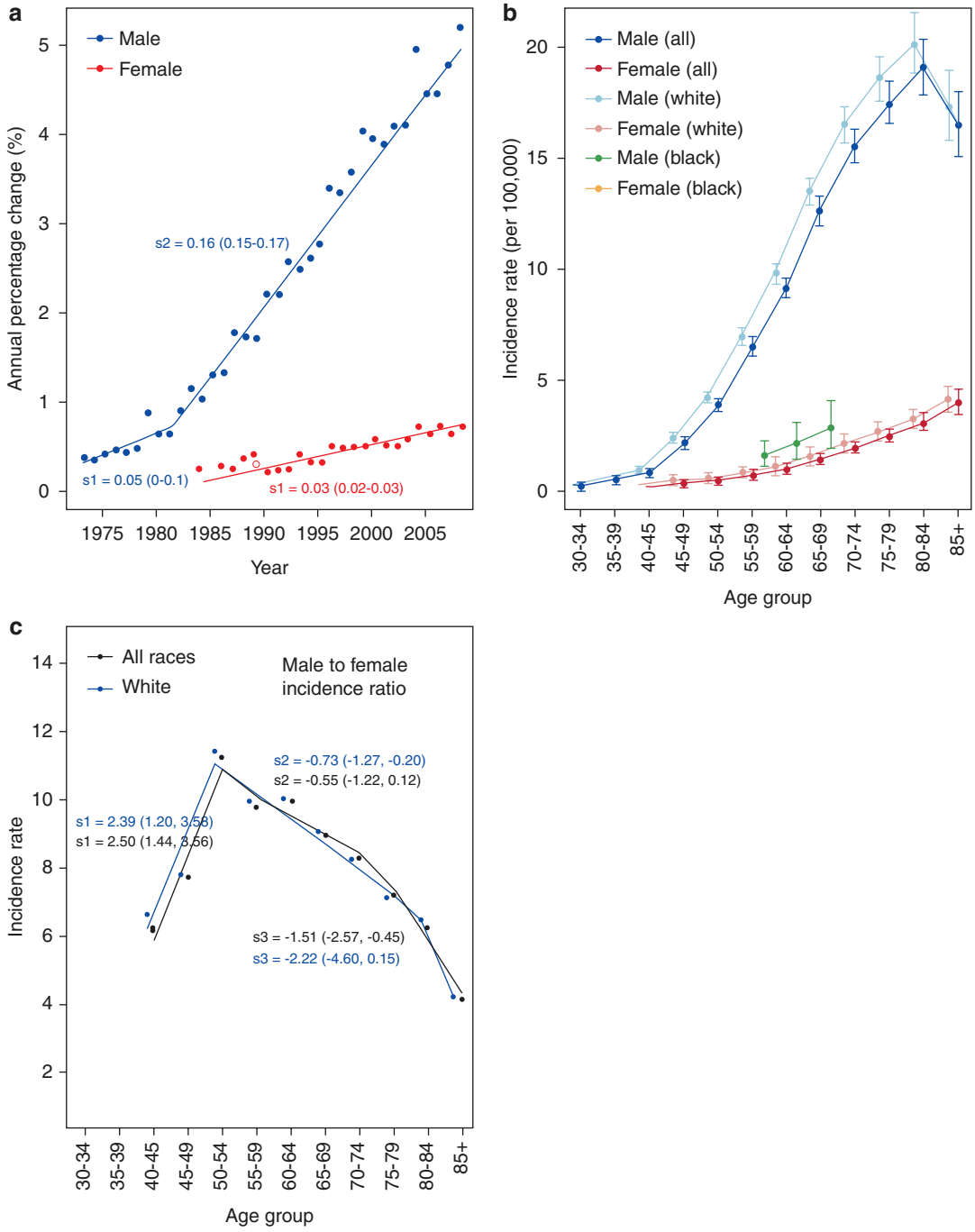

Fig. 6.7 The different incidence of esophageal adenocarcinoma depending on sex. (**a**) Esophageal adenocarcinoma annual percentage change (APC) versus year by sex. (**b**) Incidence rates (per 100,000) of esophageal adenocarcinoma listed across age groups by sex. Mean and 95% CI were generated from Surveillance, Epidemiology, and End Results (SEER) 9 database and indicated via points with error bar spread. (**c**) Black solid line (all races) and blue solid line (white only) indicates the predicted value of male-to-female incidence ratio by age after fitting regression models with joint point approach on all races of esophageal adenocarcinoma patients. Fitted slopes with 95% CI were indicated next to the lines (adapted from Mathieu et al. [88])

patients who receive long-term sex hormonal therapy. No significantly increased risk of EAC has been observed in patients with breast cancer using adjuvant antiestrogen tamoxifen therapy [93–96]. Interestingly, however, two register-based studies have found a decreased risk of EAC in patients with prostate cancer who might have received anti-androgenic treatment [97, 98] although an earlier study did not [99]. Sex hormones exert their biologic effects through the ligation to nuclear receptors (i.e., the estrogen receptors alpha [ERα] and beta [ERβ] and the androgen receptors [ARs]). These sex steroid hormones, predominantly estrogens in female and androgens in male, demonstrate sex/gender-specific concentration profiles [28]. These hormones regulate cell growth and behavior via a variety of estrogen and androgen receptor subtypes which are distributed widely throughout normal and abnormal human tissues, including cancers. The role of sex hormones in the development of prostate and breast cancers is well known [100, 101]. ARs are also widely expressed in human tissues and have been identified in EC [50, 51, 102–104]. Furthermore, circulating testosterone and DHT were higher in patients who develop BE, the precursor lesion for EAC, even after controlling age, BMI, and GERD symptoms. Regarding estrogens ERα is predominantly expressed in female sex organs, such as the breast, uterus, and ovaries, and is responsible for estrogen-reduced mitogenic signaling in epithelial cells in these organs [105]. In contrast, ERβ exists not only in sex organs but also in a wide range of organs in both sexes [106] and has been found to be expressed in EAC tissues and adjacent normal esophageal mucosa [107, 108]. Previous studies have shown decreased ERβ expression in various cancer tissues as compared with benign tumors or normal tissues [109]. Possible mechanisms of the inhibition of ERβ on EAC include induction of cell cycle and growth arrest and initiating apoptosis in cancer cells through ER ligands [110]. The expression of ARs has also been confirmed in EAC tissue [51, 103], and possible mechanisms for androgens/AR involvement in the regulation of esophageal cancer growth are considered. In addition androgen may induce overexpression of fibroblast growth factors or members of their receptors, which have an important role in hormone-dependent malignancies [103]. Biological actions of androgens and testosterone-activated extra-nuclear signaling pathways [28] are similar to the ERβ pathway. That is, testosterone molecules translocate via the plasma membrane and are transformed into DHT by 5α-reductase [28]. Then DHT binds to the AR and heat shock protein (HSP) is then released. Ligand-AR complexes can be phosphorylated (and/or are modified by other post-translational mechanisms) and these ligand-AR complexes form homodimers and move into the nucleus [28]. In the cell nucleus ligand-AR complexes bind to specific DNA elements-androgen-responsive elements (ARE), which are in target gene promoters. A large variety of co-factors and regulators can orchestrate AR-induced gene transcription. Testosterone binds to undefined membrane-associated androgen receptor(s) (mAR) that might transduce signaling downstream to phospholipase C (PLC) [28]. Activation of PLC produces several second messengers including Ins(1,4,5)P3 (IP3) and diacylglycerol (DAG). Ca^{2+} influx then leads to an increase in intracellular Ca^{2+}. In addition, testosterone binds to the membrane-associated receptor, which associates with and activates Src kinase [28].

The levels of all androgens increase at puberty and peak during adolescence and then gradually decrease with age [111]. Androgen deficiency in aging males associated hormonal changes are gradual, with bioavailable testosterone levels declining 2–3% annually from approximately 30 years of age [112, 113]. There is at least a tenfold difference in testosterone levels between males and females of reproductive age [28]. The plasma concentration of the hormone in males is between 10 and 35 nmol/L and in females is 0.7–2 nmol/L [114]. The SEER dataset has shown a peak sex ratio of 11:1 in favor of males in the 50–54 years age bracket, but falling to 4:1 in the 75–79 year age group [88]. Furthermore, in vitro evidence from cell culture work and subsequent testing in murine models

suggests a significant influence of sex hormones upon cancer growth and that this effect is consistent with expression patterns of the receptors. However, the identification of ARs in human tissue specimens has been less straightforward, with expression reported by some authors, but not by others [28]. While androgens and their receptors probably do play a role in the carcinogenesis of EC, more work is required to evaluate this role and to understand their contribution to the genesis of EC [28]. Although therapeutic implications and novel therapies are desirable, there is currently insufficient evidence to support a clinical trial of androgen deprivation therapy in this cancer [28].

6.3.2.2 Reflux Esophagitis and Barrett's Esophagus

The prevalence of GERD in the Western population is about 10–20% and about 30–60 million people in the United States. This entity is capable of producing EAC directly or, more commonly, through an intermediate pre-neoplastic lesion, BE. The increased incidence of BE in the last 30 years is correlated with an increased incidence of EAC in the same period. BE is a pre-malignant lesion that develops in 6–14% of patients with GERD and of which, around 0.5–1% will develop adenocarcinoma [78]. In a study performed in Spain, the incidence of adenocarcinoma during follow-up of patients with BE was 0.48% per year (95% CI, 0.006–2.62%), for an incidence of 1 per 210 patient-years [115]. The largest study is a nationwide, population-based, cohort study conducted in Denmark, involving all patients with BE during the period from 1992 through 2009, using data from the Danish Pathology Registry and the Danish Cancer Registry [116]. The study included 11,028 patients with BE for a median of 5.2 years [116]. The incidence rate for EAC was 1.2 cases per 1000 person-years (95% CI, 0.9–1.5) [116]. As compared with the risk in the general population, the RR of EAC among patients with BE was 11.3 (95% CI, 8.8–14.4) and the annual risk of EAC was 0.12% (95% CI, 0.09–0.15) [116]. Current surveillance guidelines assume a risk for EAC of 0.5–1%, far from the results obtained in this study. Detection of low-grade dysplasia was associated with an incidence rate for EAC of 5.1 cases per 1000 person-years compared to 1.0 case per 1000 person-years among patients without dysplasia. These data question the rationale for ongoing surveillance in patients who have BE without dysplasia [116]. A male-predominant sex bias including reflux esophagitis (RE), BE, and EAC allude to sex/gender differences in the vulnerability or resistance of the esophageal epithelium to caustic compounds of gastroduodenal contents [88, 117]. Decreased estrogen after menopause might be related with the raise in the incidence and severity of RE [117]. The esophageal barrier function is important for the protection against reflux substance in RE [118–120]. Chronic exposure to gastric acid and other intraesophageal materials such as bile and alcohol can disrupt the esophageal barrier function [120, 121]. Reduced levels of 17β-estradiol due to aging, especially during women's menopause, can potentially increase epithelial permeability and microbial translocation [119]. Recent studies suggested that estrogen can increase esophageal mucosal resistance by upregulating the expression of esophageal tight junction protein such as occludin. Such mechanism of estrogen might explain the male predominance of RE [120–122]. Honda et al. [120] have conducted an animal study to identify the role of estrogen treatment on esophageal epithelial barrier function and found that 17β-estradiol administration reduced the dilation of the intercellular space caused by luminal irritants. Moreover, 17β-estradiol administration increased the expression of occludin [120]. Adhesion between esophageal neighboring cells could be enhanced by estrogen which can potentiate the expression of the integral tight junction protein [122]. Lack of these protective effects of estrogen in male could possibly explain the higher prevalence of RE in male than female [120]. Close relation between female's reproductive hormone and the severity and prevalence of RE have been reported [123]. During postmenopausal period, the prevalence of GERD spectrum has raised rapidly. However, it is lower than that in male during the reproductive age [124].

6.3.2.3 Obesity

Obesity is a major and consistent risk factor for the development of EAC. It has become a serious public-related disease in developed countries. By 2015, an estimated 75% of the American people will be overweight (BMI > 25) and 41% obese (BMI > 30). The OR of developing adenocarcinoma is 1.52 (95% CI, 1.33–1.74; $p < 0.0001$) for those with BMI in the 25–30 rank compared with those who have normal weight. A high BMI (>25) was associated with an increased risk of EAC (males, OR 2.2; 95% CI, 1.7–2.7; females, OR 2.0; 95% CI, 1.4–2.9) [125]. Higher levels of BMI were associated with increased risk of EAC (overweight males, OR 1.8; 95% CI, 1.5–2.2; obese males, OR 2.4; 95% CI, 1.9–3.2) [126]. Two main mechanisms have been proposed for the development of EAC in obese patients. First, obesity is a risk factor for increasing the incidence of RE, and second obesity provokes a hormonal dependent mechanism which is mainly mediated by inflammatory markers secreted from adipocytes [78]. In several high-income countries (e.g., the United States, Australia, France, and the United Kingdom), incidence rates of EAC are rising rapidly in part because of increased obesity and waist circumference [127].

6.3.2.4 Smoking and Alcohol

Alcohol is not related to the presence of EAC, but smoking tobacco is a known risk factor, with an OR of 2.7 (95% CI, 1.64–4.45) relative to non-smokers [128]. Tobacco smoking is associated with an increased risk of EAC in both sexes, but these associations are weaker than the associations with ESCC [13, 79] (Table 6.1). A pooled analysis of 12 population-based studies found an approximately twofold increased OAC risk in ever smokers compared with non-smokers with an exposure-response pattern in terms of increasing pack-years [129]. Smoking cessation has been associated with a slight reduction of EAC risk. A recent meta-analysis of 23 studies revealed that compared to never-smokers, the risk estimates of EAC were only slightly weaker in former smokers (relative risk [RR] 1.60; 95% CI, 1.48–1.85) than in current smokers (RR 2.34; 95% CI, 2.04–2.69), and a risk reduction was seen only in participants who had stopped smoking over 20 years ago (RR 0.72; 95% CI, 0.52–1.01) [56].

6.3.2.5 Nutritional Factor

In a Swedish population study, an inverse relationship was found between intake of total dietary fiber and the presence of adenocarcinoma of the gastroesophageal junction [79]. Similarly, in a US case-control study, it was found that a diet rich in vitamins, fruits, and vegetables protect against the development of this disease [78]. However, in general evidence regarding dietary factors influencing EAC risk remains inconclu-

Table 6.1 Risk factors of squamous cell carcinoma and adenocarcinoma of esophagus (adapted from Arnal et al. [79])

Risk factor	Squamous cell carcinoma	Adenocarcinoma
Geography	Southeastern Africa, Asia, Iran, South America	Western Europe, North America (United States), Australia
Race	Black > white	White > black
Gender	Male > female	Male > female
Alcohol	++++	–
Tobacco	++++	++
Obesity	–	+++
GERD	–	++++
Diet: low fruits and vegetables	++	+
Socioeconomic conditions	++	–
Genetic aspects	++	+

GERD gastroesophageal reflux disease, + associated risk, – no risk associated

sive. Studies have revealed a decreased risk of EAC associated with higher intake of fruit and vegetables, dietary fibers, and some dietary supplements, i.e., β-carotene and vitamins C and E [130]. However, the World Cancer Research Fund Continuous Update Project for EC, which was based on findings from cohort studies only, recently concluded that no dietary aspect had strong evidence for an association with EAC risk, except for limited evidence of a reduced EAC risk associated with vegetable intake [18].

6.3.2.6 Drugs

Observational studies with a large number of patients showed that the use of non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and statins in patients with BE reduced the progression to adenocarcinoma [78]. The most studied agents have been acid suppressants. Our team also reported frequent regression of BE by PPI treatment which was supported by the immunohistochemical detection of mucin phenotype, grade of specialized intestinal metaplasia (SIM), Ki67, and CDX2 expression in Barrett's mucosa [131]. A systematic review with meta-analysis of studies evaluating the association between PPIs and histamine receptor antagonists (H2RAs) and risk of EAC or high-grade dysplasia (HGD) in patients with BE has been recently published [78]. The authors identified seven observational studies (2813 patients with BE, 317 cases of EAC or HGD, 84.4% PPI users). On meta-analysis, PPI use was associated with a 71% reduction in risk of EAC and/or HGD in patients with BE (adjusted OR 0.29; 95% CI, 0.12–0.79) [78]. There was a trend toward a dose-response relationship with PPI use for >2–3 years protective against EAC or HGD (three studies; PPI use >2–3 years vs. <2–3 years: OR 0.45; 95% CI, 0.19–1.06 vs. OR 1.09; 95% CI, 0.47–2.56), but considerable heterogeneity was observed [78]. Two studies reported the association between H2RA use and risk of EAC and/or HGD (1352 patients with BE, 156 cases of EAC, 25.4% on H2RAs), but they did not show a significant effect [132]. The largest study was published short after and challenged these results. In such nationwide case-control study carried out in Denmark, no cancer-protective effects from PPIs were seen [133]. In fact, among 9883 patients with a new diagnosis of BE, the authors identified 140 cases with incident EAC and/or HGD, with a median follow-up time of 10.2 years [133]. The relative risk of EAC or HGD was 2.2 (95% CI, 0.7–6.7) and 3.4 (95% CI, 1.1–10.5) in long-term low and high adherence PPI users, respectively [133]. Such results could partly be due to confounding by indication or a true negative effect from PPIs. Based on these results, continuous PPI therapy might not be necessary in all patients with BE to prevent the progression to EAC and could be directed at symptom control [133].

6.3.2.7 Genetics

Although the rapidly increasing incidence of EAC in Western populations does not indicate a prominent role of genetic factors in the etiology of EAC, it has been estimated that up to one third of EAC cases may be attributable to a combination of germline mutations [134]. GWAS have identified a number of genetic variants associated with an altered risk of EAC or BE, including those which may be associated with embryonic development of the esophagus, oncogenic activity, and body fat regulation [135–140]. However, the associations with individual SNPs have been modest with no more than a 20% increase in EAC risk [13]. The most significant results were not only for cancer but also for pre-cancer BE, suggesting that much of the genetic basis for EAC lies in the development of BE, rather than its to EAC [79]. They found three novel genome-wide significant loci for EAC and BE combined and extended existing findings at the *FOXF1* and *HLA* loci. One of the novel regions is chromosome 3p13, near FOXP1, a gene encoding a transcription factor, which regulates esophageal development [80]. Interestingly, two of the other regions (*BARX1/9q22.32* and *FOXF1/16q24.1*) contain risk-associated SNPs which disrupt binding of FOXP1 [79]. Further dissection of these loci is likely to lead to insights into the etiology of this rapidly fatal cancer [79, 136] (Table 6.1).

6.3.3 The Effect of Hormone Replacement Therapy on the Esophageal Adenocarcinoma and Its Prognosis Defending on Age and Sex

Several studies observed moderately reduced risk estimates associated with the use of hormone replacement therapy in postmenopausal women, and a recent meta-analysis based on five observational studies found a 25% decreased risk of EAC in postmenopausal women compared with nonusers (RR 0.75; 95% CI, 0.58–0.98) [141]. However, none of the previous studies supported a reduced risk of EAC associated with use of oral contraceptives [142–144]. Recent studies also suggest a decreased risk of EAC associated with higher intake of dietary phytoestrogens, including lignans, quercetin, resveratrol, and flavonoids [145–147]. These findings indicate a potential useful role of chemoprevention of EAC if the sex hormone hypothesis could be further confirmed [27].

A large pooled analysis using prospective randomized trial data showed sex difference in the treatment and prognosis [1]; 3265 patients were included for survival analysis (2668 [82%] male, 597 [18%] female; 2627 (80%) < 70 years, 638 (20%) > 70 years) [1]. A significant improvement in overall survival (OS) (HR 0.78; $p < 0.001$) and disease-specific survival (DSS) (HR 0.78; $p < 0.001$) was observed in females compared with males [1]. No significant differences in OS (HR 1.11; $p < 0.045$) or DSS (HR 1.01; $p < 0.821$) were observed in older patients compared with younger patients [1]. For patients who underwent resection, older patients (15% vs. 10%; $p < 0.03$) and female patients (14% vs. 10%, $p < 0.10$) were more likely to achieve favorable Mandard TRG scores [1]. Actually EAC are predominantly a disease of older age with more than half of new cancers each year being diagnosed in people aged older than 75 years in the United Kingdom [148, 149]. However, there is usually discrepancy in the use of treatment options compared with younger patients, and outcomes are generally poorer for older patients [150, 151]. The attribution of effects is complicated however by the increased impact of comorbidities in the elderly population, making it difficult to ascertain the reason for poorer outcomes in this patient group outside of clinical trials [1]. Similar to the differences in drug handling observed between males and females, pharmacokinetic factors such as changes in body composition, reduced hepatic capacity, and reduced renal perfusion [152] can also vary with increasing age, regardless of comorbidities, and may influence drug distribution, metabolism, and clearance. During chemotherapy, females experienced significantly more grade III nausea (10% vs. 5%; $p < 0.001$), vomiting (10% vs. 4%; $p < 0.001$), and diarrhea (9% vs. 4%; $p < 0.001$) than males, suggesting that females had significantly improved survival while experiencing more gastrointestinal toxicities [1].

6.4 Conclusions

EC shows striking sex difference with males having a higher incidence and poorer outcomes, while some of the differences in cancer incidence may be due to behavioral factors such as smoking and/ or hormonal influences. ESCC is still the most common histological type in the world and the highest incidence are found in Africa and the Middle East. There has been a shift from ESCC to EAC in fundamental areas of Europe such as Norway and the United Kingdom, in the United States, and in Australia. The reasons for the strong male predominance in EAC remain to be explained, but recent molecular evidence suggests the role of sex hormones. That is, estrogen has preventive effect and androgens provoke EAC, explaining this sex difference of EAC. Furthermore, the risk factors for ESCC and EAC are different. That is, tobacco smoking and excessive alcohol use are the main established risk factors for ESCC, particularly in Western populations, while tobacco smoking only moderately increases the risk of EAC and alcohol does not influence this risk of EAC. Smoking cessation substantially reduces the risk of ESCC but has only a limited effect in the prevention of

EAC. GERD and obesity are the main risk factors for EAC, and anti-reflux therapy seems to prevent EAC in the long term. Dietary factors may influence the risk of EC, particularly fruit and vegetables, but existing evidence remains limited. Genetic factors may have limited influence on the risk of developing EC. More research efforts should be made for a better understanding of the etiology of EC in terms of sex/gender difference to support evidence-based prevention of this deadly cancer in both the developed and developing parts of the world.

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Part V

Stomach

Functional Dyspepsia

7

Nayoung Kim

7.1 Introduction

Dyspepsia is one of the most common gastrointestinal (GI) diseases, accounting for 5% of patients diagnosed at primary care centers. Patients with dyspepsia report various symptoms such as epigastric heartburn, epigastric pain, postprandial discomfort, and bloating. These symptoms are usually chronic, lowering patients' quality of life (QoL) and increasing their social burden. Most patients with dyspepsia are diagnosed with functional dyspepsia (FD), which refers to a cluster of chronic and reoccurring GI symptoms, mainly in the upper GI tract, in the absence of an organic disease with a clear causal link, such as peptic ulcer, GI malignancy, gastroesophageal reflux disease (GERD), and pancreatic and biliary tract diseases. In South Korea, organic diseases were identified in 8–20% of patients with dyspepsia who were referred to tertiary hospitals from primary care centers, while 70–92% of the patients have FD [1]. FD is one of the most common functional gastrointestinal disorders (FGIDs), along with irritable bowel syndrome (IBS) [2] (Table 7.1). FD is often caused by interpersonal stress, which results in gender differences and a higher prevalence in women who are sensitive to stress. Many studies have dealt with gender differences in IBS, but in light of recent reports of similar trends in FD, it is important to understand the epidemiology of FD in relation to gender, clinical trends, and QoL; such research will shed light on the distribution of FD subtypes, economic costs, treatment, drug development, and medical resource allocation [3]. With this background, this chapter explores gender differences in the epidemiology, pathophysiology, and clinical trends of FD.

7.2 Definition of Functional Dyspepsia

With the expanding understanding of FD in the 1990s and later, a classification system of FD became necessary for research and clinical treatment, and the Rome Foundation was established. Given the absence of research-based standards or evidence, diagnostic criteria were established by reaching a consensus through the Delphi approach. As new data were gathered with time, more evidence-based approaches were included as suggestions. The Rome I diagnostic criteria (1994), Rome II diagnostic criteria (2000), and Rome III diagnostic criteria (2006) were published sequen-

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Table 7.1 Rome IV functional gastrointestinal disorders published in 2016 (adapted from Drossman and Hasler [2])

A. Esophageal disorders	
A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	
B. Gastroduodenal disorders	
B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome (PDS)	B3a. Chronic nausea vomiting syndrome (CNVS)
B1b. Epigastric pain syndrome (EPS)	B3b. Cyclic vomiting syndrome (CVS)
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome (CHS)
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	
C. Bowel disorders	
C1. Irritable bowel syndrome (IBS)	C2. Functional constipation
IBS with predominant constipation (IBS-C)	C3. Functional diarrhea
IBS with predominant diarrhea (IBS-D)	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits (IBS-M)	C5. Unspecified functional bowel disorder
IBS unclassified (IBS-U)	C6. Opioid-induced constipation
D. Centrally mediated disorders of gastrointestinal pain	
D1. Centrally mediated abdominal pain syndrome (CAPS)	
D2. Narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia	
E. Gallbladder and sphincter of Oddi (SO) disorders	
E1. Biliary pain	E2. Functional pancreatic SO disorder
E1a. Functional gallbladder disorder	
E1b. Functional biliary SO disorder	
F. Anorectal disorder	
F1. Fecal incontinence	F3. Functional defecation disorders
F2. Functional anorectal pain	F3a. Inadequate defecatory propulsion
F2a. Levator ani syndrome	F3b. Dyssynergic defecation
F2b. Unspecified functional anorectal pain	
F2c. Proctalgia fugax	
G. Childhood functional GI disorders: neonate/toddler	
G1. Infant regurgitation	G5. Functional diarrhea
G2. Rumination syndrome	G6. Infant dyschezia
G3. Cyclic vomiting syndrome (CVS)	G7. Functional constipation
G4. Infant colic	
H. Childhood functional GI disorders: child/adolescent	
H1. Functional nausea and vomiting	H2a2. Epigastric pain syndrome
H1a. Cyclic vomiting syndrome (CVS)	H2b. Irritable bowel syndrome (IBS)
H1b. Functional nausea and functional vomiting	H2c. Abdominal migraine
H1b1. Functional nausea	H2d. Functional abdominal pain—NOS
H1b2. Functional vomiting	H3. Functional defecation disorders
H1c. Rumination syndrome	H3a. Functional constipation
H1d. Aerophagia	H3b. Nonretentive fecal incontinence
H2. Functional abdominal pain disorders	
H2a. Functional dyspepsia	
H2a1. Postprandial distress syndrome	

tially, and the Rome IV diagnostic criteria were published in 2016. Research on the concepts and pathophysiology of FD is continuing, so further updates regarding the conceptual definition and diagnostic criteria of this disease are expected.

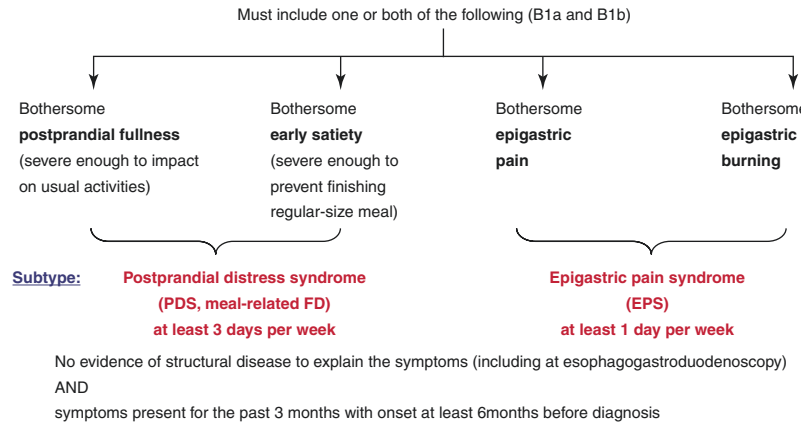

Fig. 7.1 Definition of functional dyspepsia: Rome IV criteria (adapted from Stanghellini et al. [4])

The definition of FD [4] in the Rome IV diagnostic criteria published in 2016 added the term "bothersome," referring to the disease's impact on everyday life, and symptom frequency per week from the definition of FD [5] in the Rome III diagnostic criteria published in 2006 [4] (Fig. 7.1). FD is diagnosed if patients experience symptoms including epigastric pain from the stomach or duodenum, epigastric burning, postprandial fullness, and early satiation that started at least 6 months ago and continued for the past 3 months without clear organic, systemic, or metabolic cause identified on upper GI endoscopy, imaging tests (e.g., epigastric ultrasound), and various clinical pathology tests [4, 5]. More specifically, epigastric pain refers to pain or substantial discomfort felt in the epigastrium, which is the area below the breastbone and above the navel; epigastric burning refers to a burning sensation in the epigastrium; postprandial fullness refers to discomfort from feeling like food is lingering in the stomach after a meal; and early satiation refers to the status of not being able to finish a meal due to feeling like the stomach is full shortly after starting a meal despite not having consumed a full meal. The Rome III diagnostic criteria named the ulcerative subtype as epigastric pain syndrome (EPS) and the functional disorder subtype as postprandial distress syndrome (PDS) based on the results of various studies, and it was hypothesized that these two clusters of symptoms have slightly different disease mechanisms and treatment directions. PDS is diagnosed when patients feel bloated after consuming a regular meal portion more than three times a week or when patients are not able to finish a regular meal due to the aforementioned early satiation. Additional diagnostic criteria that indicate PDS are discomfort in the epigastrium, nausea after a meal, or excessive burping, which can also be present in EPS patients. In contrast, EPS refers to intermittent pain at a modest to severe level or soreness limited to the epigastrium. The pain should not be limited to other parts of the stomach or chest and should not spread, ameliorate with defecation or passage of gas, or meet the diagnostic criteria for gallbladder and sphincter of Oddi disorders. An additional diagnostic criterion that indicates EPS is pain that ameliorates or deteriorates with food consumption or that can occur when the stomach is empty, which can also be present in PDS patients [4].

7.3 Epidemiology and Prevalence of Functional Dyspepsia

The prevalence of FD, based on large cohorts around the world, is 10–30% [6]. The prevalence varies by diagnostic criteria, region, sex, and age [4]. Population-based studies [7–10] that excluded structural diseases using endoscopic findings reported that FD was 1.36–2.71 times more prevalent among women than among men. Similarly, women had higher prevalence rates in all large studies of participants in health check-ups [11–13]. Based on a 2016 meta-analysis that reported a prevalence of 25.3% in women,

which was higher than the prevalence of 21.9% in men, it can be understood that FD is more common among women [14]. The prevalence of FD was found to be higher among women in the United States, Western Europe, Southeast Asia, and the Middle East, but this trend was not found in South America, Australia, and Africa [14]. A possible reason for this discrepancy might be that the analysis was based on hospital patients. In a study based on online surveys using the Rome IV diagnostic criteria in the United States, the United Kingdom, and Canada, the prevalence was higher among women than among men for all ages under 65, but this trend was not seen in ages over 65, which indicates the potential relevance of decreasing levels of female hormones or changes in sociocultural roles in old age [15]. The results of multivariate analyses of risk factors of FD vary by study [16]. The risk factors of FD reported in some studies are female gender, low body mass index, old age, *Helicobacter pylori* (*H. pylori*) infection, smoking, history of non-steroidal anti-inflammatory drug (NSAID) use, and low education level [14, 17–19]. In a multicenter study with participants of health check-ups, female gender and an education level lower than a university degree were identified as risk factors for FD [13]. When the data were analyzed by age and gender, an education level lower than a university degree was a risk factor for males, while female gender was a significant risk factor among those younger than 60 [14]. Therefore, it is necessary to analyze the risk factors for FD according to age and gender. Abuse history is especially common among female patients [20–22], and when such abuse occurs in childhood (i.e., when the brain areas that control stress and nociception develop), the risk of FD and the severity of symptoms increase [20]. In such patients, delayed gastric emptying is especially relevant [23].

7.4 Symptoms of Functional Dyspepsia

When the symptoms of FD of men and women are compared, men generally report soreness, while women report discomfort [24–29]. When women with FD experienced epigastric pain, it was closely associated with anxiety [3], and women with a history of gynecological surgery had more severe epigastric pain than women without a history of gynecological surgery [3]. Women experienced epigastric pain for a longer duration than men [30], with greater severity, and many women had relevant psychological factors [31, 32]. However, some studies did not find such differences, indicating that the results depend on the circumstances of each study [3, 30, 33–35]. It is common for GERD to exist together, which is referred to as the overlap syndrome of FGID [12, 36–38]. The mechanism is not clearly known, but it has been hypothesized that the overlap syndrome of FGID occurs due to common pathophysiology including visceral hypersensitivity or mobility disorder, issues in the brain-gut axis, and psychological issues [39]. Among patients with the overlap syndrome of FGID, young female patients more often had GERD and FD together [40]. According to a report from China, patients with IBS and FD were more likely to be women, be divorced or widowed, and have IBS symptoms such as bloating, having difficulty defecating, and experiencing diarrhea and constipation at the same time [41]. QoL was especially low in patients with the overlap syndrome of FGID [39, 40, 42], and when the overlap syndrome of FGID involved the esophagus, stomach, and colon, QoL was low regardless of age and gender [43]. The social and environmental aspects of the QoL of FD patients are particularly impaired, suggesting the need for early treatment [3, 44], but related studies are scarce. One certain fact is that depression and anxiety symptoms are more severe and QoL is lower among women with FD than among men with FD [3, 44, 45]. In a community-based case-control study conducted in Sweden, women with FD had significantly lower QoL, including physical domain, physical role limitation, physical pain, and overall health awareness, than men with FD [45]. In an Asian study with FD patients reporting poor QoL, the risk factors were identified as female gender, depression and anxiety symptoms, old age, severe symptoms, and low education level [44]. Patients with somatization disorder or psychological risk factors such as a history of physical sexual abuse visited hospitals more frequently [46]. However,

no gender differences were found in a Taiwanese study that used the Rome I or II diagnostic criteria [12], suggesting that differences may exist across countries and cultures.

7.5 Pathophysiology of Functional Dyspepsia

The disease mechanism of FD includes altered gastric motility, visceral hypersensitivity, brain-gut axis, low-grade gastritis, *H. pylori* infection, and genetic, social, and psychological factors, but no single factor explains FD in a satisfactory manner. Gender differences have also not been studied sufficiently [31, 47]. This section explains the main pathophysiology of FD, focusing on gender differences in the disease mechanism.

7.5.1 Sex Hormones

Estrogen is directly and indirectly involved in motor and sensory control via GI immunity, endocrine and nervous pathways, and the intestinal microbiota [48]. A well-known example of the role of estrogen is slower digestive activity during the luteal phase than during the follicular phase and in pre-menopausal women than in men [23, 49, 50]. Estrogen or the combination of estrogen and progesterone is known to interfere with the gastric emptying rate [51–53]. Estrogen acts on neurotransmitters to affect pain reaction in pain recognition pathways [54]. Estrogen also influences women's emotions and moods, causing premenstrual, postpartum, and menopausal depression through extreme mood changes after menopause, ovariectomy, or delivery [55, 56]. Taken together, female sex hormones seem to play a causal role in FD by influencing visceral pain and gastric motility [16].

7.5.2 Visceral Hypersensitivity

Visceral hypersensitivity is an important pathological mechanism of FD. The causes of hypersensitivity related to EPS are sensitization after inflammation or infection and amplification during central nervous system processing. Upregulation or sensitization of transient receptor potential vanilloid-1 (TRPV1), which is a capsaicin receptor, is hypothesized to play an important role in GERD, FD, and IBS. When capsaicin, which is the spicy component of hot chili peppers, combines with TRPV1, it activates afferent C-fiber nerves, causing a burning sensation and pain. In a clinical trial where capsaicin capsules were randomized, patients with FD reported moderate to severe symptoms with smaller amounts of capsaicin and had more symptoms than healthy controls, demonstrating that for a significant proportion of patients, FD is related to visceral sensory hypersensitivity via the TRPV1 pathway [57]. TRPV1 is controlled by neurotropic factors such as nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF) that are increased by inflammation, and TRPV1 can also be activated in acidic environments [58]. Therefore, research has explored the relationships between FD and the TRPV1 pathway, inflammation due to *H. pylori* infection, and acidity. It was hypothesized that expression of TRPV1, NGF, and GDNF would be high in women with FD who have high visceral hypersensitivity; however, visceral pain-related mRNA gene expression was found to be higher in men with FD than in those without FD, but no such difference was found in women, among whom depression and anxiety symptoms were more important factors instead [3]. In women, visceral hypersensitivity can increase and cause FD without visceral pain-related gene expression when depression and anxiety are present, but among men, the mechanism involves increased expression of visceral pain-related genes.

7.5.3 Psychological Distress

Data suggest an association between emotions and visceral function, and common psychiatric disorders among FD patients are anxiety disorder, depression, and somatization disorder. Compared to healthy controls, FD patients have higher scores for anxiety, depression, neurosis, tension, hatred, and health anxiety, but it remains unclear whether these psychoneurotic disorders

cause FD. The fact that no specific characteristic of FD can be found suggests that no single characteristic plays a significant role in the pathogenesis of FD. Stress is defined as the state of threatened homeostasis or disharmony, and its causes are classified as interoceptive stressors (e.g., intestinal infection, mucosal inflammation, and visceral bleeding) and exteroceptive stressors (e.g., psychological stress). The brain reacts to stimuli from the abdominal viscera. In healthy individuals, interoceptive input is generally not consciously recognized, but the control of input can change due to stress and activity of the excitatory circuit, which affects the abdominal viscera through feedback. Sometimes disruption of inter-organ interactions of the brain and the abdominal viscera can occur and sensitize the pain threshold to cause FD due to severe psychic trauma, especially, in the early childhood. However, this disruption caused by psychic trauma can be healed through central and peripheral neuroplastic changes [59] (Fig. 7.2). Neuroplastic changes refer to neurogenesis or regrowth of neurons when the scars heal after psychological shock severe enough to cause post-traumatic stress disorder, such as sexual abuse or experience of war, damage the hippocampus, or destroy cortical cells [59]. This concept indicates that emotional changes caused by internal or external stimuli can result in physiological changes and affect

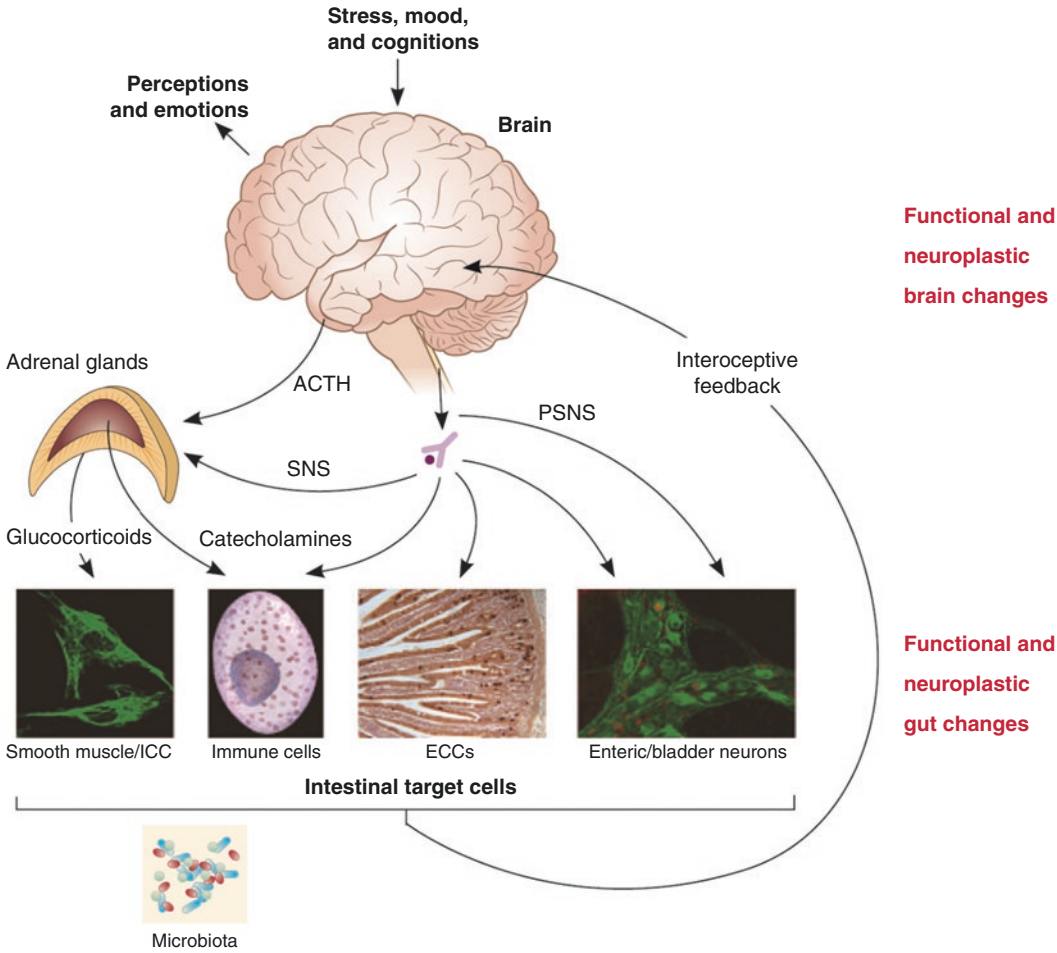

Fig. 7.2 Bidirectional brain-visceral interactions. Disruption of the inter-organ interaction of the brain and the abdominal viscera can cause central and peripheral neuroplastic changes (adapted from Mayer and Tillisch [59])

health. There is a general consensus that important life events or emotional conflicts can cause GI pain or other GI symptoms, and research on gender differences in this process is being actively conducted.

7.5.4 Brain-Gut-Microbiome Axis and Gender Differences

The terms "brain-gut axis" or "gut-brain axis" were used frequently in the past, but more recently, as the role of the gut microbiome has been emphasized, the concept of brain-gut-microbiome axis is being established. Since disturbances in the brain-gut-microbiome axis can cause FD, gender differences in the brain-gut-microbiome axis have been examined in this section.

7.5.4.1 Brain Response to Stress

Responses to stress hormones are slightly different by gender. Women are more vulnerable to the corticotropin-releasing factor (CRF) and the locus coeruleus (LC)-norepinephrine system, which increases sensitivity to stress [60]. Among men, even when CRF is oversecreted, the response to CRF is weakened through the cellular internalization of CRF receptors, but this internalization does not occur in women; as a result, stress is transmitted to the whole body instantly [60]. Estrogen also acts on estrogen receptor alpha (ERα) in the hypothalamus to prevent the negative feedback of cortisol, which influences women's vulnerability to stress [60]. Thus, when women are exposed to severe and constant stress, they are vulnerable to stress, as the CRF-related component of the endocrine system and the arousal system are not controlled [60]. As a result, women report somatization disorders that often co-occur with severe FD [16, 61] (Fig. 7.3). These differences in CRF function affected drug development. For example, CRF antagonists can be expected to have an intense impact on women [60]. Other than CRF connectivity, gender differences have been reported in altered functional connectivity of the amygdala, which controls postprandial satiety, food intake, emotion regulation, and endogenous pain suppression. There have been many reports of functional or structural

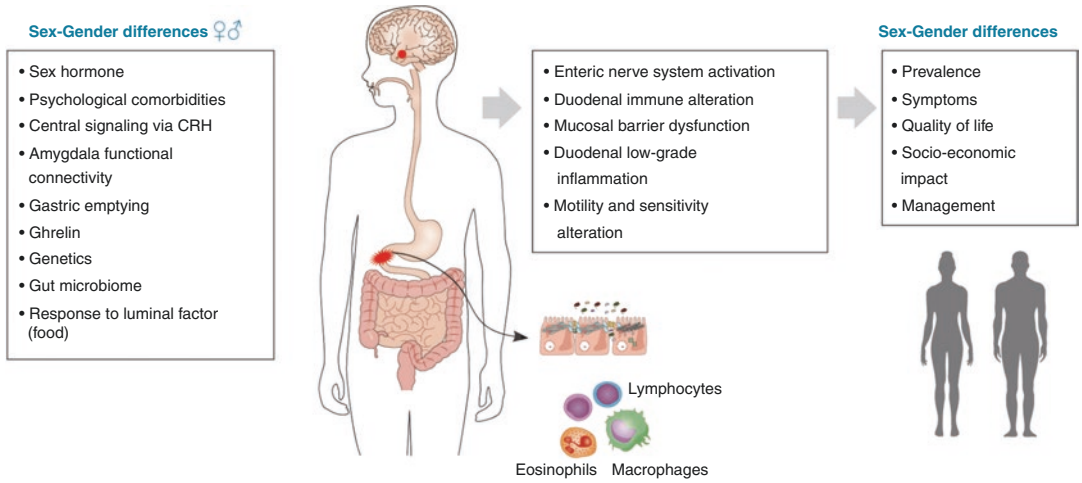

Fig. 7.3 Sex/gender differences in the disease mechanism of functional dyspepsia. Sex/gender differences in sex hormones, brain signal transmission through corticotropin-releasing factor (CRF), altered functional connectivity of the amygdala, ghrelin, genetics, gut microbiome, diet that affects the enteric nervous system, duodenal immune system, mucosal barrier function, low-grade duodenal inflammation, and intestinal motility and sensitivity are determinants of sex/gender differences in functional dyspepsia. Such differences influence the epidemiology of functional dyspepsia, symptoms, quality of life, socioeconomic impact, and treatment (adapted from Kim and Kim [16])

differences in the default mode network and salience network in brain areas of FD patients by gender [61–64]. Particularly in women with FD, severe disruptions in cognitive-affective processing in the amygdala were reported [61]. When brain imaging of the basolateral area of the amygdala (BLA) among women with FD was compared to those of women controls and men with FD, the insular resting-state functional connectivity (rsFC) was higher, while the medial prefrontal cortex and lateral and dorsal lateral prefrontal cortex rsFC were lower [61]. These results indicate that visceral afferent circuits are more strongly activated and negative emotions are increased in women patients with FD [61]; as a result, women are more sensitive to pain than men and report digestive pain/discomfort more frequently.

7.5.4.2 Gut Microbiota

The gut microbiota, immune cells, enteroendocrine cells, and the enteric nervous system have a complex interrelationship; regardless of the cause, disorders of the gut microbiota are known to contribute to FD [65]. The term "microgenderome," which emphasizes the interrelationship between the gut microbiota and sex hormones, has recently been proposed [66]. There are no gender differences in the gut microbiome until puberty, when differences in the gut microbiome start to develop [67]. The discovery that the composition of the gut microbiota among women becomes similar to that among men after menopause [68] has drawn attention to the effects of sex hormones on the gut microbiota. Differences in the gut microbiota by gender have been reported in studies investigating gender, age, and region in cohorts in the United States, the United Kingdom, Columbia [69], and Japan [70], developing the evidence base for age and gender differences in the gut microbiota. I also reported a review regarding the factors which affect the gut microbiota and the interplay of microbiota and GI diseases in terms of sex and gender differences [71]. Evidence for an association between gut microbiota and sex hormones was strengthened by the discovery that the gut microbiota influence the concentration of estrogen by deconjugating conjugated estrogen excreted in bile and reabsorbing it through the enterohepatic circulation [72]. What, then, is the effect of the gut microbiome on FD? Given that mice pups separated with their mother after birth demonstrate symptoms of depression and anxiety and their symptoms improve when they are fed microbes beneficial for these symptoms, there seems to be a close association between the gut microbiome and the brain. Studies on FD and the gut microbiota have been published [73–75], and in a clinical study where rifaximin, an antibiotic that is not absorbed by patients with FD, was administered in a randomized manner, symptoms of FD improved. The improvement was especially noticeable in women, demonstrating a gender difference in the treatment effect of rifaximin for FD [73]. It was hypothesized that the symptoms improved due to the influence of rifaximin on the microbes distributed in the duodenal mucosa, but more studies are needed to investigate the mechanism through which the gut microbiome affects FD in men and women.

7.5.5 Gastroduodenal Dysfunction and Ghrelin

GI distension and gastric emptying disorders are commonly observed in patients with FD [76, 77]. A gastric emptying study using the ^{13}C-acetate exhalation test showed that gastric emptying took longer among women than among men, and women with FD reported gastric reflux symptoms more frequently, indicating that gastric emptying disorders contribute to GERD [78]. The mechanism of decreased gastric emptying function is not understood in detail beyond its association with sex hormones, but based on the fact that women rate pain as more intense than men given the same pressure and volume of GI distension, it can be inferred that women's stomachs are more sensitive and responsive to smaller gastric content [79]. In addition, studies using barostats found that the gastric accommodation reflex time was longer in women than in men [80], indicating an association with vagal tone [79]. Ghrelin is a digestive hormone that promotes appetite and stomach movement [81–83].

When acylated ghrelin levels decrease, gastric emptying function is reduced [84], which causes vomiting or FD [25, 85]. No difference was found in fasting plasma acylated ghrelin levels between healthy participants and FD patients, but ghrelin levels were associated with self-reported digestive symptom scores among women with FD [86]. However, in a comparative study of patients with the PDS subtype and healthy controls conducted by the author's research team, plasma acylated ghrelin levels were lower in male patients than in healthy controls, but this difference was not found among women [3]. Similarly, mRNA expression for *TRPV1* and *GDNF*, which are visceral pain-related genes, was found to be higher in men with FD, while depression and anxiety symptoms were more important factors in women with FD [3]. Taken together, these results indicate that there are gender differences in both the symptoms and pathophysiological mechanisms of FD.

7.5.6 Genetic Factors

Since there are familial trends in FGIDs, it has been hypothesized that there are genetic factors beyond the environmental factors to which all family members are exposed, and genetic research about FD has explored this possibility [31, 87]. It has also been hypothesized that the frequent occurrence of the overlapping syndrome, in which multiple FGIDs co-occur, suggests a high probability of sharing similar genetic polymorphisms. Genes with genetic polymorphisms that govern GI functions can be classified into three broad categories, as follows:

A. Neurotransmitters
    1. Serotonin
    2. Cholecystokinin (CCK)
    3. VIP
    4. Substance P
    5. α2 adrenergic receptors
B. Cytokine
    1. Pro-inflammatory: TNF-α, interferon
    2. Anti-inflammatory: TGF-β1, IL-10
C. Corticotropin-releasing factor (CRF)

Many studies have investigated associations between single-nucleotide polymorphisms (SNPs) of genes related to neurotransmitters and FD, but due to the nature of such studies, contrasting findings have been reported [88]. The author also published SNP-related results about FD in 2014, in a study finding that the S/S genotype of serotonin promoter gene *SLC6A4* 5-HTTLPR had a negative correlation with *H. pylori*-positive EPS [89]. The C/C genotype of *TRPV1* 945G>C had a negative correlation with both EPS and PDS, and the correlation was stronger when patients were *H. pylori*-positive [89]. That study suggested the importance of genetic factors in the pathogenesis of FD through SNPs, underscoring the necessity of future studies investigating the mechanism underlying the relationship between this SNP and *H. pylori* infection. No associations were found between the *GNB3* 825C>T, *ADRA2A* -1291C>G, and *CCK-1R* intron 779T>C SNPs and FD [89]. There were gender differences in this genetic tendency. According to a Japanese report, the association between the *COX-1*-1676T allele and EPS was found only in women but not in men [87]. However, more studies are required to draw conclusions about gender differences in genetic polymorphisms and FD.

7.5.7 Low-Grade Duodenal Inflammation and Tight Junction Proteins

Duodenal mucosa permeability is increased in FD patients [90], and this increase in permeability has been hypothesized to cause symptoms of FD by inducing hypersensitivity toward fat, capsaicin, and acid [91]. Tight junction proteins (zona occludens, occludin, claudin 1, claudin 2, claudin 4, etc.) play an important role in protecting the intestinal mucosa; therefore, issues in tight junction protein expression cause disturbances in the protection of the duodenal mucosa. Studies have reported that sex hormones can influence this process [92, 93]. A study conducted by the author's research team also found that expression of *CLDN2* mRNA, which encodes a

tight function protein, was significantly lower in men with FD than in healthy male controls regardless of *H. pylori* infection. This difference was not found among women with FD, indicating that issues in claudin 2 are related to the pathophysiology of FD among men [94].

7.5.8 Food

It is standard to recommend that FD patients avoid smoking cigarettes, drinking alcohol, taking NSAID medication, drinking coffee, and consuming spicy food. However, there is no evidence suggesting that tobacco or alcohol consumption causes chronic FD. Coffee, as a non-specific stimulant, can directly or through gastric reflux cause heartburn, but there is no evidence of direct associations between coffee or tea and FD. These studies may not have stratified participants by gender. A recent study on FD and food reported that symptoms were caused by consuming wheat and gluten regardless of the subtype of FD, while fat caused PDS [95]. An examination of gender differences in the symptoms of FD and food indicated that women reported postprandial satiety more frequently than men, and it is also well-known that women crave food more [96]. It has also been reported that vasovagal reflex occurs more easily in women, who respond differently to lipoprotein than men [96]. Gender differences in physiological reactions to food consumption may furnish explanatory evidence for gender differences in FD. According to a study on the association between symptoms of chronic dyspepsia and glycemic index (GI) or glycemic load (GL) by gender, symptoms were caused by high GI or GL in men and participants in the normal weight group, but not in women and participants in the overweight group [97]. Gender differences were found in a randomized, parallel design study on the postprandial response to consuming delicious and comforting food [96]. As ongoing research is adding details to our understanding of this issue, it is expected that additional studies in the future will shed further light on gender differences in the impact of food on FD.

7.6 Treatment of Functional Dyspepsia

Since most patients with FD have non-severe and sporadic symptoms, their symptoms tend to improve when they are told that they do not have a severe disease, which provides some degree of psychological comfort. However, some patients are difficult to treat as they do not respond to various treatments. Especially for female patients who have underlying anxiety or depression or who have severe anxiety about the symptoms themselves, it is very effective for the doctor to listen attentively to their descriptions of their symptoms and to help patients identify stressors. A tailored treatment approach based on understanding gender differences in the pathogenesis of FD is necessary.

7.6.1 Rapport Between Patients and Doctors

The placebo effect of medication is very high (20–70%) for FD, and this placebo effect is usually derived from the rapport that patients have in doctors. Therefore, patients' trust in doctors is vitally important. Trust can be built through the following process, which is especially important for female patients.

A. Understand the reason why the patient visited the doctor and look for what the patient is concerned about and fears specifically.
B. Do not demonstrate a critical attitude toward the symptoms that the patient reports; instead, listen carefully and perform an examination.
C. Explain the necessary diagnostic process to investigate patients' concerns. Excessive testing should be avoided unless there are changes in symptoms or it is absolutely necessary.
D. Provide an explanation emphasizing that FD is not "neurotic" and that patients are not experiencing symptoms in the absence of a disease. In other words, FD is not a fictional disease—it really exists.

E. Explain the pathophysiology of FD, including digestive tract motility, visceral hypersensitivity, and the brain-gastrointestinal interrelationship.
F. Help establish realistic goals and allow patients to find their own disease management behaviors, including adjustments in lifestyle and symptom tolerance, since the symptoms of FD are repetitive and chronic.
G. Explain that the medication used does not cure the disease, but rather helps in symptom improvement.

7.6.2 Adjustments to Lifestyle and Diet

The extant evidence on lifestyle and diet adjustments is insufficient, but it is generally recommended that patients avoid coffee, spicy food, fat, excessive drinking, and smoking and maintain a regular schedule and adequate amount of exercise. Food, emotional events, and environmental factors that cause or exacerbate symptoms should be identified and avoided. The principle of diet adjustments is to avoid foods that cause or exacerbate symptoms.

7.6.3 Medication

Medications for FD overall have a slight advantage over placebo, and since there are various disease mechanisms of FD, it is difficult for one medication to be effective for all patients [98]. There are also gender differences in pharmacokinetics [99]. Women have reduced drug metabolism as they generally have longer gastric emptying time, lower gastric pH levels, and smaller body mass but a larger plasma volume, higher body-fat ratio, and lower cytochrome P450 enzyme activity level. Due to these differences, women more frequently report medication side effects, especially in pregnancy, menopause, and old age [99]. This section summarizes the gender differences in treatment effects for patients with FD.

7.6.3.1 *H. pylori* Eradication

It was recently reported that extensive infiltration of $CD8^+$ and $CD4^+$ T cells or macrophages accompanies *H. pylori* infection and that symptoms continue even after *H. pylori* eradiation among patients with *H. pylori*-positive FD, in whom mucosal infiltration of inflammatory cells was still observed; these findings indicate that *H. pylori* infection plays a role in FD. There were no differences in *H. pylori* prevalence between the FD group and healthy control group [100], posing difficulties for this explanation. However, as reports found that symptoms of FD ameliorated after eradicating *H. pylori* [17, 100], chronic gastritis due to *H. pylori* infection has been highlighted as the mechanism of FD. In other words, it is difficult to explain FD in all patients in terms of *H. pylori* infection, but chronic gastritis due to *H. pylori* infection is the cause of FD in some patients, who should be identified. The 2014 Kyoto consensus suggested that patients should be classified as having FD due to *H. pylori* infection when their symptoms ameliorate after *H. pylori* eradication and remain resolved for 6–12 months [101]. The reason why *H. pylori* eradication is suggested first for FD in various guidelines, including guidelines from the Asia Pacific, the United States, Canada, and Japan, is that several randomized controlled trials have reported positive results regarding the effects of *H. pylori* eradication [102–108] (Table 7.2).

A 2019 meta-analysis of 18 randomized controlled trials on *H. pylori* eradiation treatment among patients with FD reported a risk ratio (RR) of 1.18 (95% confidence interval [CI], 1.07–1.30; $p < 0.01$) in the eradication group compared to the control group [109]. There was moderate heterogeneity ($I^2 = 34\%$) in the studies, and the number needed to treat (NNT) was 15.0 [109]. Symptom improvement was related to whether the *H. pylori* prevalence was below 50% or above 50%. No significance was found in studies conducted in Asia, where the *H. pylori* prevalence is above 50% (RR 1.14; 95% CI, 0.99–1.33; $p = 0.08$; $I^2 = 37\%$). In studies conducted by the author's research team, symptoms of FD improved after *H. pylori* eradication, but the

Table 7.2 Randomized controlled trials on the effects of *H. pylori* eradication in functional dyspepsia patients (since 2000)

Authors	Year	Enrolled studies	Follow up	Number	Symptom improvement	OR (95% CI)	NNT
Gisbert et al. [102]	2002	9 RCT	At least 6 months	Patients; 953 Control; 958	Eradication group; 43% (95% CI, 40–46%) Control group; 39% (95% CI, 36–42%)	1.20 (0.91–1.58)	25
Moayyedi et al. [103]	2006	17 RCT	At least 3 months	Patients; 1934 Control; 1632	Eradication group; 36% (range 15–75%) Control group; 29% (range 7–51%)	0.90 (0.86–0.94), 10% relative risk reduction (95% CI, 6–15%) in eradication group	14
Jin et al. [104]	2007	7 RCT	At least 1 month	Patients; 395 Control; 366	Eradication group; 74.4% (294/395) Control group; 47.3% (173/366)	3.61 (2.62–4.98)	NM
Zhao et al. [105]	2014	14 RCT	At least 12 months	Patients; 1490 Control; 1503	Eradication group; 40.6% (605/1490) Control group; 34.0% (511/1503)	1.38 (1.18–1.62)	15

OR odds ratio, *CI* confidence interval, *NNT* number needed to treat, *RCT* randomized controlled trials, *NM* not mentioned

response was not favorable in female patients [17, 110]. Possible explanations include a longer gastric emptying time [111], accompanying psychological symptoms [56, 112], and more frequent symptoms of FD [113], rather than inflammation due to *H. pylori* infection, among women. An interesting fact is that the mean values from the ^{13}C-urea breath test, which is related to the concentration of *H. pylori* bacteria, were higher in women than in men [114]; this trend, which has been observed in patients with FD [115], may suggest gender differences in *H. pylori*-host interactions.

7.6.3.2 Proton Pump Inhibitors

Most studies have found that gastric acid secretion is normal in patients with FD, but it was observed that when acid contacts the duodenal mucosa, the proximal stomach is relaxed and becomes sensitive to stomach expansion, indicating that gastric acid may be the cause of gastritis and duodenitis in some patients. It has also been reported that proton pump inhibitors lead to significant symptomatic improvement in patients with FD, especially epigastric pain syndrome. According to a community-based cohort observational study investigating the effects of proton pump inhibitors, men responded better than women, and psychiatric medication was more effective in women [116]. This finding is in line with the mechanism of FD, through which men are affected more strongly by TRPV1 or ghrelin and women by anxiety and depression.

7.6.3.3 Prokinetics

A systematic meta-analysis of the randomized controlled studies that support the guidelines for FD in the 2017 joint guidelines issued by the American College of Gastroenterology and the Canadian Association of Gastroenterology (ACG/CAG) reported that prokinetics were effective regardless of subtype (EPS or PDS) (RR 0.81; 95% CI, 0.74–0.89; I^2 = 91%; NNT, 7) [108]. In terms of gender and sex difference, there were gender differences in prokinetics that demonstrated effectiveness for IBS, such as the 5-HT_3 antagonist alosetron and the 5-HT_4 agonist tegaserod [56], but there have been no studies on gender differences in the effect of prokinetics on FD. Since the gender differences in the mechanisms of FD can be explained by men being more affected by TRPV1 or ghrelin and women by anxiety and depression, it is expected that the effect of prokinetics on FD will be greater in men.

7.6.3.4 Antidepressants

Several studies have investigated tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) [31, 117]. In a meta-analysis of 1241 patients in 13 randomized controlled studies, antidepressants were effective in treating FD [118]. Another multicenter randomized controlled study reported that amitriptyline, but not escitalopram, appears to benefit some patients with FD, particularly those with ulcer-like (painful) FD [119]. However, patients with delayed gastric emptying did not respond to these drugs [119]. In these two studies, there were no analysis regarding the sex/gender differences of treatments. Augmentation therapy, in which a drug with a different mechanism is added to enhance the effect, has recently received attention as another treatment strategy for depression for patients with severe symptoms. The idea is to maximize effectiveness and minimize side effects [120]. Many studies have suggested gender differences in the effectiveness of TCAs and SSRIs on depression [121–125]. For example, fluvoxamine, which is an SSRI, was more effective among young women than among men or women over the age of 44. It is hypothesized that estrogen affects serotonin synthesis and activity by binding with serotonin receptors [125]. Multiple other studies found that women responded better to SSRI antidepressants than men [126–129], which may reflect the fact that FD is more closely related to depression and anxiety among women. However, further studies are needed due to inconsistent results; for instance, a recent study found no gender differences in the effect of low-dose antidepressants on intractable FD [123].

7.6.3.5 Targeting the Gut Microbiota

A recent study found that the concentration of microbiota in the duodenal mucosa was correlated

with the symptom severity of FD, suggesting that antibiotics may be helpful for patients with FD [130, 131]. Rifaximin, an antibiotic that is not absorbed, has been reported to improve the gut microbiome and thereby improve inflammation in the intestine and reduce visceral hypersensitivity [130, 132]. A randomized study in China found that overall symptoms of FD, postprandial discomfort, and burping improved in a rifaximin group compared to a placebo group among patients with FD excluding those with IBS [73]. It is interesting that postprandial discomfort and overall symptoms of FD improved in a lasting manner among women compared to among men [73]. The exact mechanism needs additional research. In a study of yogurt containing *Lactobacillus gasseri* OLL2716 and FD, symptoms improved in patients with postprandial distress syndrome, but no gender-stratified analysis was conducted, possibly due to the small sample size [133].

7.6.3.6 Psychotherapy

Psychotherapy can be an effective treatment for FD. Therefore, for patients who do not respond to medication at all, have psychiatric diagnoses or experience difficulty in conducting everyday routines, or have somatization disorder, it is advisable to seek a psychiatric consultation. Augmentation therapy is used frequently in psychiatry [106] (Table 7.3), because various factors cause FD and the effects of psychiatric medication can differ by brain area [106, 120]. Since the brain structure is different in men and women and symptoms of FD are influenced by depression and anxiety more among women than among men, it is expected that psychotherapy will be more effective among women.

Table 7.3 Medications used in augmentation therapy (adapted from Sperber and Drossman [106])

Central drug with central drug	SSRI with TCA
	SNRI with SSRI
Central drug with peripheral drug	SSRI with anticholinergic
	TCA with pregabalin or gabapentin
Non-pharmacological treatment with central drug	Hypnosis with TCA
	CBT with SSRI
Non-pharmacological treatment with peripheral drug	Hypnosis with anticholinergic
	CBT with pregabalin or gabapentin
Central drug with non-pharmacological treatment and peripheral drug	Hypnosis with SSRI and anticholinergic agent
	CBT with SNRI and pregabalin

SSRI selective serotonin reuptake inhibitor, *SNRI* selective noradrenaline reuptake inhibitor, *CBT* cognitive-behavioral therapy

7.7 Conclusions

FD affects up to 16% of otherwise healthy individuals in the general population [134]. Researchers have recently begun to understand that men and women have different symptoms and responses to treatment for each disease, and tailored medicine is entering the spotlight, increasing the interest in sex-/gender-specific medicine. In most studies of FD, an important FGID, it has been consistently reported that the prevalence is higher in women than in men, patterns of symptoms are different, and FD has a particular impact on women's QoL. Risk factors of FD include psychological comorbidity, acute gastroenteritis, female sex, smoking, use of NSAIDs, and *H. pylori* infection [134]. The pathophysiology remains incompletely understood, but it is probably related to disordered communication between the gut and the brain, leading to motility disturbances, visceral hypersensitivity, and alterations in GI microbiota, mucosal and immune function, and central nervous system processing [134]. There are gender differences in the mechanism of FD [16], as brain-gut axis related factors such as depression and anxiety play a larger role in women, whereas ghrelin and TPRV1 are more strongly implicated in men. The therapy of FD includes multimodality approach. That is, eradication therapy should be offered to patients with FD who test positive for *H. pylori*. Other therapies with evidence of effectiveness include proton pump inhibitors, histamine-2 receptor antagonists, prokinetics, and central neuromodulators [134]. Since the gender differences in the mechanisms

of FD can be explained by men being more affected by TRPV1 or ghrelin and women by anxiety and depression, it is expected that the effect of prokinetics on FD will be greater in men, similar to proton pump inhibitors. To develop effective medications, it is necessary to analyze the effect of each drug on FD by gender.

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8 *Helicobacter pylori* Infection and Gastritis

Nayoung Kim

8.1 Introduction

Since *Helicobacter pylori* (*H. pylori*) was first cultured from gastric mucosa in 1983, it has been found to cause not only peptic ulcers and chronic gastritis but also malignant gastric mucosal lymphoma and gastric cancer. Thus, peptic ulcers, which had been classified as an intractable disease due to complications such as frequent recurrence and bleeding, have become a treatable infectious disease. *H. pylori* is a gram-negative, spiral bacterium that infects more than 50% of the world population. The innate and adaptive immune response proceeds vigorously after exposure to *H. pylori*, but in most cases, the infection lasts for a lifetime unless artificial eradication is performed [1]. A 1998 study on the prevalence of serum *H. pylori* among all ages in South Korea reported that the prevalence increased steadily until the age of 49 (Fig. 8.1a), but when the prevalence according to sex was compared, there was no difference in *H. pylori* infection by sex until the age of 15, whereas *H. pylori* infection became significantly more common among males than among females after the age of 16 [2] (Fig. 8.1b). This phenomenon was also found in a 2016–2017 epidemiological study [3]. Males also had a higher rate of *H. pylori* eradication than females [3], but the rate of reinfection after *H. pylori* eradication was also higher among males than females [4], suggesting that the disproportionately higher *H. pylori* infection rate among males will most likely remain stable. Eighty percent of individuals infected with *H. pylori* do not experience any issues for their lifetime, but 1–3% develop gastric cancer, which is twice more prevalent among males than females worldwide. Environmental factors such as consumption of tobacco or alcohol may be responsible for this sex/gender difference, but it has been hypothesized that a partial cause is the sex/gender difference in gastritis due to *H. pylori* infection. The higher prevalence of atrophic gastritis and intestinal metaplasia among males supports this hypothesis [5]. In the past 15 years, atrophic gastritis and intestinal metaplasia decreased among females but remained steady among males [6], indicating that environmental factors such as tobacco and alcohol together with *H. pylori* infection contribute to atrophic gastritis and intestinal metaplasia. An interesting fact is that *H. pylori* infection increases the risk of metabolic syndrome [7]. Total cholesterol was significantly higher among males, while a reduction in high-density lipoprotein (HDL) cholesterol was clearly observed in females [8], indicating that the systemic effects of *H. pylori* infection are different by sex/gender. This section examines the

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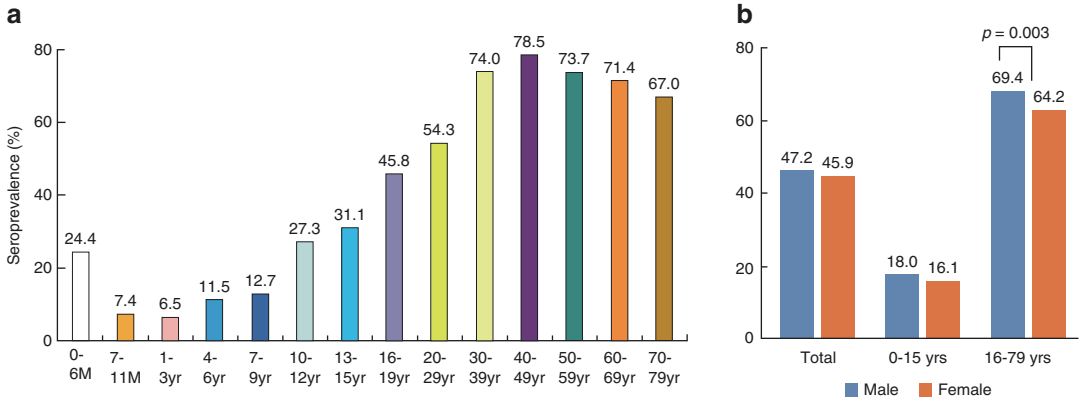

Fig. 8.1 (**a**) Prevalence of *H. pylori* by age and sex in the 1998 national epidemiological study. The prevalence of *H. pylori* increased with age and peaked in the 40–49 age group. (**b**) The serum prevalence of *H. pylori* among children younger than 16 of age and those older than 16. The prevalence among males was significantly higher than that among females in the 16 and above age group. $*p < 0.05$; *M* month, *yr* years (adapted from Kim et al. [2])

epidemiology of *H. pylori* infection, re-infection after eradication, and atrophic gastritis and intestinal metaplasia from *H. pylori* infection, as well as sex/gender differences in lipid metabolism.

8.2 Sex/Gender Differences in the Epidemiology of *H. pylori*

A research society dedicated to *H. pylori* (currently the Korean College of Helicobacter and Upper Gastrointestinal Research) conducted a study with 102 nationally gathered researchers and a total of 5732 participants (2336 individuals in the 0–15 age group and 3396 individuals in the 16–79 age group) who were asymptomatic to obtain insights into the prevalence of *H. pylori* infection in South Korea in 1998 [2, 9]. The most prominent strength of this study is that the study sample included all ages from infants according to the national demographic distribution. A high percentage (24.4%) of infants showed *H. pylori* immunoglobulin G (IgG) obtained from the mother's placenta until 6 months after birth. *H. pylori* IgG disappeared from 7 to 12 months, with a prevalence of 7.4% in this age group, and the prevalence was lowest at 6.5% from age 1 to 3 [2] (Fig. 8.1a). The prevalence increased again until it peaked at 78.5% among individuals in their 40s and decreased to 67.0% among those in their 70s [2] (Fig. 8.1a). The prevalence of *H. pylori* increased gradually from 7 months after birth to the age of 9 years (12.7%), dramatically to the 10–12 age group (27.3%), and by around 1.7% each year until the 31–40 age group (74.0%). This trend was predominantly interpreted as reflecting a cohort effect (i.e., an effect pertaining to a defined population group tracked after estimation at a certain time point) by which the infection occurs before the age of 5 and lingers for a lifetime, rather than as indicating that new infections steadily occurred [10, 11]. The prevalence did not show a significant sex/gender difference in individuals younger than 15 (18.0% among males and 16.1% among females) but was significantly higher among males than females (69.4% and 64.2%) in individuals older than 16 ($p = 0.003$) [2] (Fig. 8.1b). This finding was confirmed repeatedly in epidemiological studies conducted in 2005 [12], 2011 [13], and 2016–2017 [3], indicating that *H. pylori* infection continues to occur after the age of 15 [3] (Fig. 8.2). A multivariate analysis of risk factors related to *H. pylori* infection found that among adults (older than 16), the number of people sharing a room while growing up (during elementary or middle school age) and economic status while growing up were associated with significant differences in the prevalence of

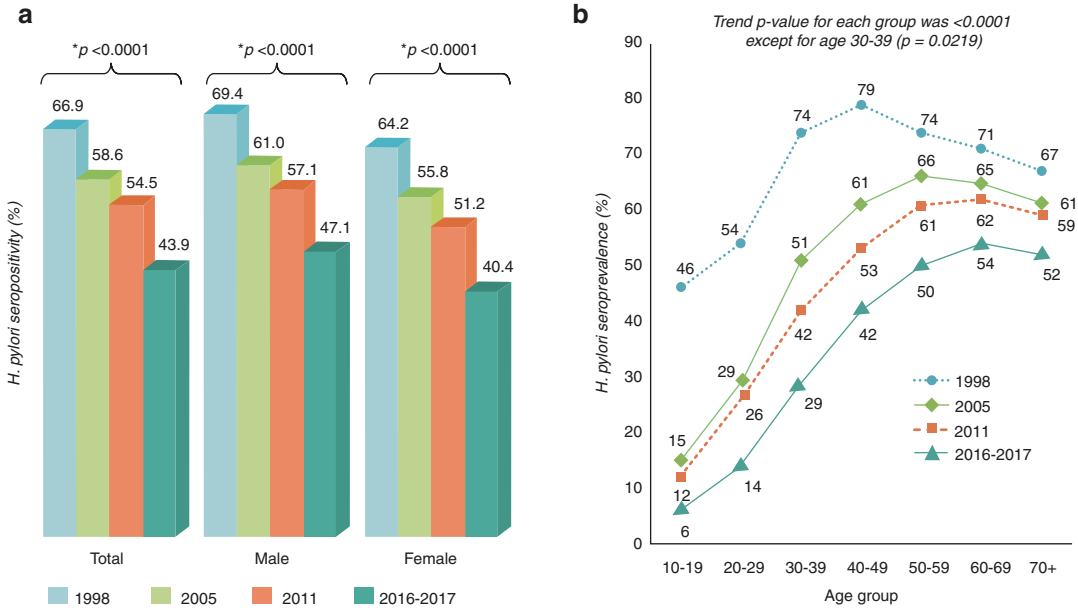

Fig. 8.2 (**a**) Changes in the serum prevalence of *H. pylori* among individuals older than 16 without a history of *H. pylori* eradication in South Korea in 1998, 2005, 2011, and 2016–2017. A sex/gender analysis shows that the prevalence was significantly higher in males than females at all four time points. (**b**) Changes by age demonstrate that the serum prevalence of *H. pylori* steadily decreased (*p for trend <0.05) (adapted from Lim et al. [3])

H. pylori infection, while among children (younger than 15), the maternal education level, household income, and drinking water showed significant associations [9]. In both children and adults, socioeconomic status and the living environment in adolescence were found to be important factors in *H. pylori* infection. This result is similar to the findings from a study conducted in Turkey among preschool-age and school-age children that reported low income, density of children per household, and use of a heater as important risk factors [14]. In other words, it can be inferred that *H. pylori* infection occurs directly from person to person due to contacts in a dense living environment and poor socioeconomic status during adolescence. Higher *H. pylori* prevalence among men older than 16 years of age than among women of the same age indicates that close contacts are more common or that hygiene is poorer among school-age boys compared to girls. Another interesting finding is that the re-infection rate after *H. pylori* eradication through the standard triple therapy including a proton pump inhibitor (PPI) was also higher among males [4]. In that study, the re-infection rate was calculated for 331 individuals who received the standard triple therapy from 2003 to 2010 and tested negative 1 year after eradication with 18–95 months of follow-up (average of 37.1 months). Risk factors for re-infection, including sex/gender, age, tobacco consumption, alcohol consumption, income, education level, digestive symptoms, atrophic gastritis and intestinal metaplasia, and resistance to clarithromycin, were analyzed. Thirty-six of the 331 participants were re-infected, reflecting a 3.51% re-infection rate per year [4]. The risk factors identified in multivariate analysis were male sex (hazard ratio [HR] 2.28; 95% confidence interval [CI], 1.05–5.00; p = 0.037) and low income (≤$5000 vs. >$5000) (HR 3.54; 95% CI, 1.08–11.67; p = 0.038) [4]. As such, the risk factors for *H. pylori* re-infection were identical to the risk factors for *H. pylori* infection, suggesting that infection and re-infection are both more active among males above the age of 16.

8.3 Sex/Gender Differences in Chronic Gastritis

Gastritis refers to inflammation found through upper gastrointestinal (GI) endoscopy or in the GI mucosa and is categorized into acute gastritis and chronic gastritis. Gastritis presenting with acute inflammation or special types of gastritis are not difficult to diagnose as they demonstrate characteristic findings on endoscopy. However, there are some controversies regarding the endoscopic diagnosis and categorization of chronic gastritis, which is the most common type. In 1936, Schindler [15] categorized types of chronic gastritis based on gastroscopy findings into superficial gastritis, atrophic gastritis, hypertrophic gastritis, and post-gastric surgery gastritis and stated that there are major differences in the disease course and prognosis according to the type [15]. As endoscopy developed after the 1980s, researchers suggested various categorizations, most of which were based on histopathological characteristics rather than gross findings. The Sydney categorization [16], which was revised in 1996, has relatively detailed descriptions of the endoscopic diagnostic criteria of gastritis, but it has not been widely used due to its limits in expressing endoscopic findings and its complexity. After *H. pylori* was first cultured in 1983, *H. pylori* infection was found to be an important cause of peptic ulcers and a cause of gastritis. The finding that chronic active inflammation of the gastric mucosa is observed in most patients with *H. pylori* infection increased interest in chronic gastritis.

8.3.1 Sex/Gender Differences in the Distribution of Chronic Gastritis

The largest study about the distribution of gastritis was based on endoscopic findings among 25,536 individuals who received upper GI endoscopy at 40 hospital health check-up centers around South Korea from January to June 2006, conducted by the Korean College of Helicobacter and Upper Gastrointestinal Research [17] (Table 8.1). Among the 25,535 patients who remained after excluding those who had a history of surgery due to diseases related to the digestive system or who received treatment for chronic diseases other than hypertension and diabetes, 3593 (14.1%) had normal findings while 21,942 (85.9%) had at least one finding of gastritis finding. Gastritis was diagnosed based on mucosal erythema, exudate, edema, erosion, color change, increased vascular fluoroscopy, and nodular change. Superficial gastritis was most common (7983, 31.3%), followed by atrophic gastritis (6918, 27.1%), erosive gastritis (6054, 23.7%),

Table 8.1 Characteristics of 25,536 participants who received upper gastrointestinal endoscopy at 40 hospital health check-up centers around South Korea in 2006 (adapted from Park et al. [17])

Variable category	*n*	%
Sex		
Male	15,180	59.5
Female	10,356	40.5
Age (y)		
≤39	6976	27.3
40–59	15,001	58.8
≥60	3549	13.9
Area (province)		
Seoul	9525	37.3
Gyeonggi	3085	12.1
Kangwon	1965	7.7
Chungcheong	3094	12.1
Kyungsang	3646	14.3
Cholla	3759	14.7
Jeju	462	1.8
Social habitus		
Current smoking[a]	6529	26.0
Alcohol (≥once per week)[a]	10,479	41.0
Medical history		
NSAID medication for ≥1 month[a]	1616	6.0
Antibiotics history within 1 month[a]	253	1.0
Epigastric pain or discomfort during last 1 year[a]		
Yes	12,921	51.6
No	12,143	48.4
Endoscopic findings		
Normal	3593	14.1
Superficial gastritis	7983	31.3
Erosive gastritis	6054	23.7
Atrophic gastritis	6918	27.1
Intestinal metaplasia	1811	7.1

n number of subjects
[a]Some data were missing due to incomplete record

and intestinal metaplasia (1181, 7.1%) [17] (Table 8.2). There were no sex/gender differences in superficial gastritis, which was the most common type. Superficial gastritis decreased significantly with increasing age, with a prevalence of 36.8% (2556) in the age group of 40 and below, 31.3% (4704) in the 40–60 age group, and 20.4% (723) in the above 60 age group ($p < 0.001$). Unlike superficial gastritis (Table 8.2a), erosive gastritis (Table 8.2b), atrophic gastritis (Table 8.2c), and intestinal metaplasia were more prevalent among males than females ($p < 0.001$, Table 8.2d). The prevalence was highest in the above 60 age group, demonstrating an increasing frequency with age ($p < 0.001$) [17] (Table 8.2).

Table 8.2 Distribution of gastritis among 25,536 participants who received upper gastrointestinal endoscopy at hospital health check-up centers in 2006 by sex and age (adapted from Park et al. [17])

Variable categories	*n*	%	*p*-value[a]
a. Superficial gastritis			
Sex			
Male (*n* = 15,180)	4720	31.1	
Female (*n* = 10,356)	3263	31.5	0.483
Age (y)			
≤39 (*n* = 6976)	2556	36.8	
40–59 (*n* = 15,011)	4704	31.3	
≥60 (*n* = 3549)	723	20.4	<0.001
b. Erosive gastritis			
Sex			
Male (*n* = 15,180)	3983	26.2	
Female (*n* = 10,356)	2071	20.0	<0.001
Age (y)			
≤39 (*n* = 6976)	1396	20.0	
40–59 (*n* = 15,011)	3744	24.9	
≥60 (*n* = 3549)	914	25.8	<0.001
c. Atrophic gastritis			
Sex			
Male (*n* = 15,180)	4215	27.8	
Female (*n* = 10,356)	2703	26.1	0.003
Age (y)			
≤39 (*n* = 6976)	1039	14.9	
40–59 (*n* = 15,011)	4335	28.9	
≥60 (*n* = 3549)	1544	43.5	< 0.001
d. Intestinal metaplasia			
Sex			
Male (*n* = 15,180)	1262	8.3	
Female (*n* = 10,356)	549	5.3	<0.001
Age (y)			
≤39 (*n* = 6976)	187	2.7	
40–59 (*n* = 15,011)	1187	7.9	
≥60 (*n* = 3549)	437	12.3	<0.001

[a]*p*-values for χ^2 test

8.3.2 Sex/Gender Differences in Atrophic Gastritis and Intestinal Metaplasia

Chronic inflammation damages cells and transforms them into various stages. Precancerous tissues associated with chronic inflammation are characterized by neutrophils, macrophages, monocytes, mast cells, eosinophils, dendritic cells, and lymphocytes, which form the tumor microenvironment [18]. The inflammation-related cells that compose the tumor microenvironment produce cytokines, reactive oxygen, and reactive nitrogen and become involved in the initiation, promotion, and metastasis of cancerous mutations [18]. These factors contribute to carcinogenesis by promoting cellular mutations and modifying the functions of enzymes and proteins in tissues by damaging cellular DNA, RNA, and proteins through chemical reactions such as oxidation, nitrogenation, and halogenation. Many factors are known to cause gastric cancer, but the most important factor is *H. pylori* infection. Other factors include old age, male sex, family history of gastric cancer, salty food, smoked food, tobacco consumption, alcohol consumption, atrophic gastritis, and intestinal metaplasia [19]. Many studies have been published on the gastric cancer risk posed by atrophic gastritis and intestinal metaplasia. For example, gastric cancer incidence was 4.9 times higher among *H. pylori*-positive atrophic gastritis patients than among *H. pylori*-positive patients without atrophic gastritis and 14.5 times higher than among *H. pylori*-negative patients without atrophic gastritis [20, 21]. The risk was even higher among patients with intestinal metaplasia. The incidence of gastric cancer among *H. pylori*-positive intestinal metaplasia patients was 6.4 times or 10.9 times higher than that among *H. pylori*-positive patients without intestinal metaplasia [21, 22], suggesting that atrophic gastritis and intestinal metaplasia

are important precancerous lesions of gastric cancer. A 2011 national multicenter study with 4023 participants who received health check-ups at 8 medical centers in South Korea confirmed the 2005 results that atrophic gastritis and intestinal metaplasia in endoscopic findings were more prevalent among males than females [5] (Tables 8.3 and 8.4). In this national multicenter study, the prevalence of atrophic gastritis confirmed by endoscopy was 40.7%, and the prevalence of intestinal metaplasia was 12.5%. The most important risk factor was age, followed by sex. The prevalence of atrophic gastritis (odds ratio [OR] 1.38; Table 8.3) and intestinal metaplasia (OR 1.88; Table 8.4) was significantly higher among males than among females [5]. Another interesting finding was that in participants with a family history of gastric cancer, intestinal metaplasia (a risk factor of gastric cancer) was significantly more common (OR 1.48; Table 8.3) [5]. A Japanese study that conducted follow-up endoscopy for 17 years also found that intestinal metaplasia was more common among males than among females [23]. The gastric antral intestinal metaplasia grade from the biopsy before *H. pylori* eradication according to the Sydney system was higher among males (0.67 ± 0.94) than among females (0.44 ± 0.77) (p = 0.003). The gastric body intestinal metaplasia grade was also higher among males (0.20 ± 0.62) than among females (0.047 ± 0.21) (p = 0.0027), a difference that was consistently observed during the study duration [23].

Table 8.3 Multivariate analysis of risk factors of atrophic gastritis diagnosed in 4032 individuals who received an upper gastrointestinal endoscopy at health check-up centers in 2011 (adapted from Joo et al. [5])

Variables	B	S.E.	*p*-value	Exp(β)	95% confidence interval	
					Lower limit	Upper limit
Age (y)						
<40				1.00		
40–59	1.039	0.165	< 0.001	2.55	2.05	3.18
≥60	1.980	0.203	< 0.001	5.00	3.71	6.74
Male	0.603	0.155	< 0.001	1.38	1.17	1.64
H. pylori IgG positivity	0.377	0.112	< 0.001	1.41	1.19	1.66
Intestinal metaplasia	1.309	0.147	< 0.001	4.29	3.35	5.50
Education below college	−0.131	0.216	0.046	1.35	1.01	1.79

B estimate, *SE* standard error, *Exp(β)* odds ratio, *H. pylori Helicobacter pylori*

Table 8.4 Multivariate analysis of risk factors of intestinal metaplasia diagnosed in 4023 individuals who received upper gastrointestinal endoscopy at health check-up centers in 2011 (adapted from Joo et al. [5])

Variables	B	S.E.	*p*-value	Exp(β)	95% confidence interval	
					Lower limit	Upper limit
Age (y)						
<40				1.00		
40–59	1.150	0.205	<0.001	3.16	2.11	4.72
≥60	1.178	0.236	<0.001	3.25	2.05	5.15
Male	0.631	0.154	<0.001	1.88	1.39	2.54
H. pylori IgG positivity	0.775	0.119	<0.001	2.17	1.72	2.74
Atrophic gastritis	1.303	0.113	<0.001	3.68	2.95	4.60
Relatives of gastric cancer	0.395	0.143	0.006	1.48	1.12	1.96
Smoking	0.170	0.138	NS	1.19	0.91	1.55
Alcohol	0.112	0.131	NS	1.20	0.87	1.45
Education below college	−0.384	0.162	0.018	1.47	1.06	2.00
Consumption of dairy product	0.338	0.116	0.004	1.40	1.12	1.76

B estimate, *SE* standard error, *Exp(β)* odds ratio, *H. pylori Helicobacter pylori*

8.3.3 Sex/Gender Differences in 15-Year Changes in Atrophic Gastritis and Intestinal Metaplasia

With improvements in the socioeconomic conditions of South Korea, *H. pylori* infections have rapidly declined. When the sex/gender differences in atrophic gastritis and intestinal metaplasia diagnosed in biopsy were examined, the decline was significant among women, but no decline was found among men. This result can be interpreted as reflecting the importance of tobacco consumption, alcohol consumption, and diet beyond *H. pylori* for the incidence of atrophic gastritis and intestinal metaplasia [6]. That study was conducted among 2002 individuals from 2003 to 2018, examined atrophic gastritis and intestinal metaplasia through biopsies, and analyzed risk factors such as sex, family history of gastritis, alcohol consumption, tobacco consumption, diet, and socioeconomic status in 3 different phases (2003–2007, 2008–2012, and 2013–2018). The prevalence of *H. pylori* infection declined over the 15-year period, from 49.2% to 40.2% and 36.0% [6]. However, no significant changes were found in the prevalence of various atrophic gastritis and intestinal metaplasia grades from the histological examination of the gastric antrum and gastric body (Fig. 8.3a). Nonetheless, the grades of gastric body atrophic gastritis (p = 0.048) and intestinal metaplasia (p = 0.010) declined significantly among *H. pylori*-negative women, and the grade of gastric body intestinal metaplasia also declined significantly among *H. pylori*-positive women (p = 0.002) [6] (Fig. 8.3b). The changes in the prevalence of atrophic gastritis and intestinal metaplasia were similar to the changes in the grades of atrophic gastritis and intestinal metaplasia. When only the prevalence, rather than the grades, of atrophic gastritis and intestinal metaplasia was examined, there were no changes in the prevalence of atrophic gastritis and intestinal metaplasia among men (Fig. 8.3c), but the prevalence of atrophic gastritis (p = 0.024) and intestinal metaplasia (p < 0.001) declined significantly over the 15-year period in *H. pylori*-positive women [6] (Fig. 8.3d). These differences in the prevalence of atrophic gastritis and intestinal metaplasia are caused by differences in tobacco consumption, alcohol consumption, and diet, indicating that lifestyle habits have a major influence on gastric cancer risk factors beyond *H. pylori* infection. According to the Korea National Health and Nutrition Examination Survey conducted by the Ministry of Health and Welfare, the percentage of smokers was 38.1% among males and 6.0% among females in 2017 (http://www.index.go.kr/unify/idx-info.do?idxCd=4237), and the percentage of monthly binge drinkers was 52.7% among men and 25.0% among women (http://www.index.go.kr/unify/idx-info.do?idxCd=4238). According to national and international literature, women tend to consume more vegetables and fruit than men [24, 25]. According to a multivariate analysis of risk factors for atrophic gastritis and intestinal metaplasia, the risk of atrophic gastritis and intestinal metaplasia increased with age and *H. pylori* infection. Smokers had a particularly high risk of intestinal metaplasia in the gastric antrum [6]. In summary, *H. pylori* infection and tobacco consumption are important risk factors for chronic gastritis, and their effects accumulate over time and with age. Recent South Korean public health policy is shifting toward active interventions to prevent gastric cancer through *H. pylori* eradication therapy. The results suggest that attention should also be given to smoking cessation, moderation in alcohol consumption, and diet.

8.3.4 Sex/Gender Differences in Atrophic Gastritis and the Reversibility of Intestinal Metaplasia After *H. pylori* Eradication

The exact mechanism of intestinal metaplasia is not completely understood, but in recent studies, expression of the *CDX* gene, which codes for a specific transcriptional factor in the intestinal tract from the duodenum to the rectum, has been hypothesized as an important factor for both intestinal metaplasia itself and its progression to

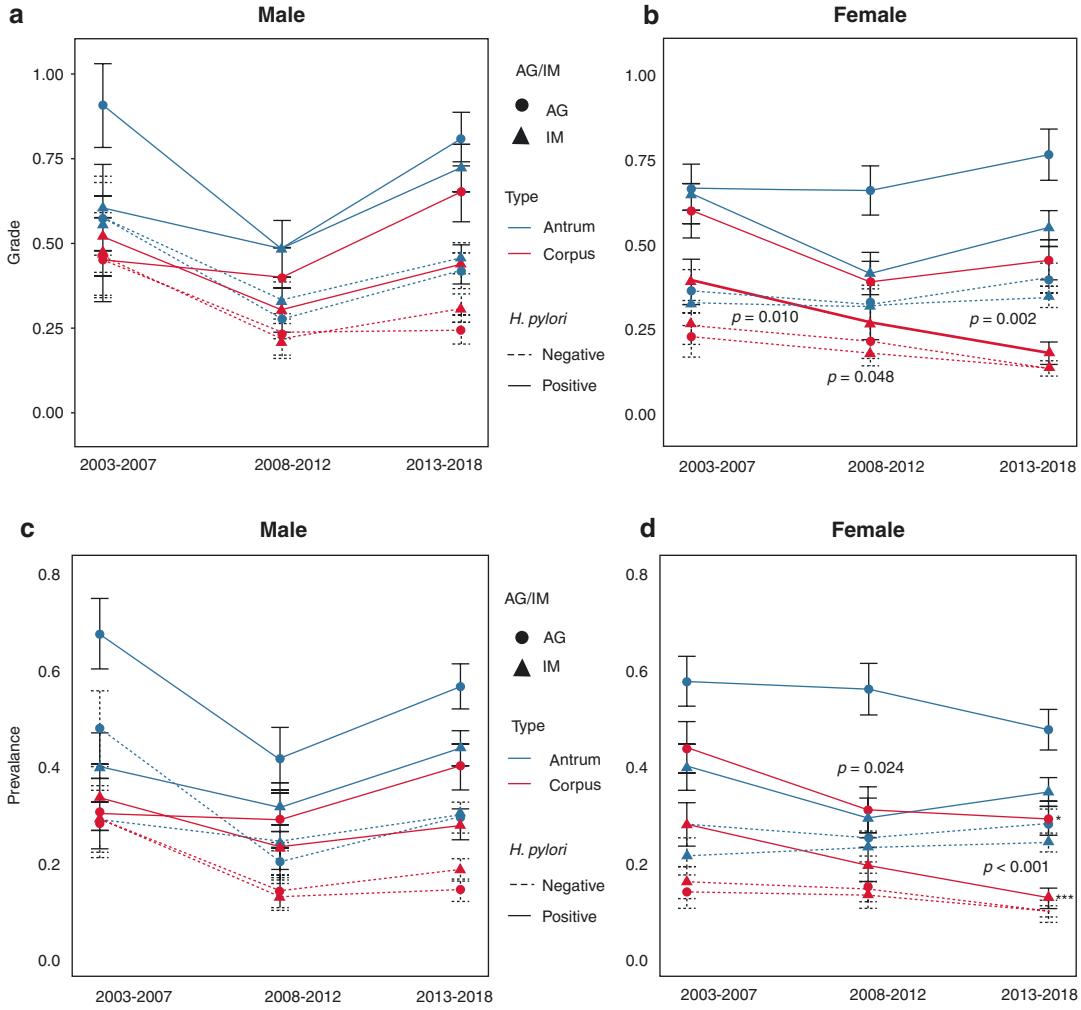

Fig. 8.3 Changes in the grade and prevalence of atrophic gastritis and intestinal metaplasia from histological examinations of the gastric antrum and gastric body in three phases over 15 years (2003–2007, 2008–2012, 2013–2018). (**a**) There were no changes in the grades of atrophic gastritis and intestinal metaplasia among men over 15 years. (**b**) Among *H. pylori*-negative women, the grades of atrophic gastritis ($p = 0.048$) and intestinal metaplasia ($p = 0.010$) in the gastric body declined significantly. The grade of gastric body intestinal metaplasia also declined significantly among *H. pylori*-positive women ($p = 0.002$). (**c**) There were no changes in the prevalence of atrophic gastritis and intestinal metaplasia among men. (**d**) The prevalence of atrophic gastritis ($p = 0.024$) and intestinal metaplasia ($p < 0.001$) declined significantly over 15 years in *H. pylori*-positive women (adapted from Kwon et al. [6])

dysplasia or gastric cancer [26]. The author investigated *CDX1* and *CDX2* gene expression using real-time polymerase chain reaction (PCR) after categorizing 270 participants by *H. pylori* infection status, intestinal metaplasia, dysplasia, and gastric cancer. *CDX1* and *CDX2* were not expressed in the normal gastric mucosa of the control group but were expressed when there was intestinal metaplasia. *CDX2* expression was also significantly higher in the gastric tissue of the *H. pylori* infection group than in the non-infected group [27]. *CDX1* and *CDX2* expression increased when the degree of intestinal metaplasia was more severe, and *CDX2* expression was significantly higher in incomplete intestinal metaplasia [27]. *CDX1* was expressed more in

the dysplasia group than in the control group, and *CDX1* and *CDX2* were both more strongly expressed in the gastric cancer group compared to the control group, supporting the hypothesis that CDX1 and CDX2, which are transcriptional factors, cause intestinal metaplasia and become involved in the mechanism of gastric cancer [27]. A study with an average follow-up of 33.7 months after *H. pylori* eradication reported that improvement in gastric body intestinal metaplasia was associated with reduced *CDX2* mRNA expression [28], providing evidence for an association between intestinal metaplasia and CDX2 and the reversibility of intestinal metaplasia through *H. pylori* eradication. In addition to endoscopic atrophic gastritis and intestinal metaplasia, histological atrophic gastritis and intestinal metaplasia were also found to be more severe among males than among females, suggesting that reversibility after eradication might be greater in females than in males.

A study analyzed a total of 24 factors that can impact the improvement of atrophic gastritis and intestinal metaplasia including environmental factors, single-nucleotide polymorphisms in host factors that regulate inflammatory responses, and genetic polymorphisms in *H. pylori* virulence factors by following up 778 participants for 10 years [29]. Since environmental factors, host factors, and genetic polymorphisms—as factors other than *H. pylori* eradication therapy or the follow-up period after therapy—contribute to improvements in atrophic gastritis and intestinal metaplasia, 11 environmental factors (sex, age, *H. pylori* infection and eradication status, tobacco consumption, history of alcohol consumption, blood type, salty food, spicy food, history of gastric cancer, education level, and economic status), 10 host genetic polymorphisms, and 3 *H. pylori* virulence factor polymorphisms were examined [29]. *H. pylori* eradication was statistically significantly associated with improvement in atrophic gastritis in the gastric antrum and gastric body, and gastric antrum intestinal metaplasia improved significantly in cytotoxin-associated gene A (*cagA*)-positive patients and patients who received *H. pylori* eradication [29]. *H. pylori* eradication was significantly associated with improvement of gastric body intestinal metaplasia [18]. When these findings were examined according to *H. pylori* infection status, *cagA* positivity and age younger than 65 were significant factors associated with improvements in atrophic gastritis and intestinal metaplasia among *H. pylori*-positive patients. In the *H. pylori* eradication therapy group, young age and economic status were significant factors associated with the improvement of atrophic gastritis and intestinal metaplasia [29]. *H. pylori* infection usually occurs at age 5 or below [30]; therefore, since the total time of exposure to *H. pylori* is shorter for younger individuals, it is suspected that atrophic gastritis and intestinal metaplasia improve more readily [29]. In order to confirm the significance of other factors excluding *H. pylori* eradication, which is the most important factor, further analyses were conducted after grouping *H. pylori*-positive patients, *H. pylori*-negative patients, and patients in whom *H. pylori* eradication was successful (Tables 8.5 and 8.6). In the *H. pylori*-positive group, age and *cagA* were significantly associated with the improvement of atrophic gastritis and intestinal metaplasia [29] (Table 8.5). Patients who were cagA antibody-positive had a significantly higher prevalence of atrophic gastritis and intestinal metaplasia [31]. Interestingly, in that study, atrophic gastritis and intestinal metaplasia showed meaningful improvement in *cagA* PCR-positive patients [29]. In the *H. pylori* eradication group, economic status had a significant influence on the improvement of atrophic gastritis, and age below 65 was a significant factor associated with the improvement of intestinal metaplasia [29]. Environmental factors such as age and economic status impact not only the incidence of *H. pylori* infection, atrophic gastritis, and intestinal metaplasia but also their improvement after eradication treatment [18]. *H. pylori* eradication was found to be a common factor that influenced the improvement of both atrophic gastritis and intestinal metaplasia, but there were factors not common to both. An explanation for this finding is that the risk factors of atrophic gastritis and intestinal metaplasia are different [18]. The risk factors of atrophic gastritis are *H. pylori* infection, old age, *H. pylori* virulence factors,

Table 8.5 Analysis of factors associated with the improvement of atrophic gastritis and intestinal metaplasia among *H. pylori*-positive patients (adapted from Hwang et al. [29])

		Improvement	No improvement	Uni-variable *p*-value	Multivariable *p*-value	OR (95% CI)
AG in antrum						
cagA	Negative (ref)	58 (50.9)	75 (68.8)			
	Positive	56 (49.1)	34 (31.2)	0.006	0.01	0.48 (0.28–0.84)
AG in body						
cagA	Negative (ref)	54 (58.1)	37 (80.4)			
	Positive	39 (41.9)	9 (19.6)	0.009	0.023	0.37 (0.16–0.87)
IM in antrum						
Age	≥ 65 years (ref)	54 (28.1)	89 (41.8)			
	< 65 years	138 (71.9)	124 (58.2)	0.004	0.017	0.55 (0.34–0.90)
cagA	Negative (ref)	88 (59.5)	108 (71.1)			
	Positive	60 (40.5)	44 (28.9)	0.035	0.072	0.64 (0.39–1.04)
IM in body						
cagA	Negative (ref)	71 (59.7)	66 (78.6)			
	Positive	48 (40.3)	18 (21.4)	0.005	0.055	0.62 (0.38–1.01)

Data are presented as number (%)
AG atrophic gastritis, *IM* intestinal metaplasia, *OR* odds ratio, *CI* confidence interval

Table 8.6 Analysis of factors associated with the improvement of atrophic gastritis and intestinal metaplasia after *H. pylori* eradication (adapted from Hwang et al. [29])

		Improvement	No improvement	Uni-variable *p*-value	Multivariable *p*-value	OR (95% CI)
AG in body						
Monthly income	<25,000 (ref)	20 (27.4)	9 (52.9)			
(dollar)	≥25,000	53 (72.6)	8 (47.1)	0.042	0.048	0.34 (0.11–0.99)
IM in antrum						
Age	≥65 years (ref)	45 (26.5)	54 (38.6)			
	<65 years	125 (73.5)	86 (61.4)	0.023	0.024	0.57 (0.35–0.93)

Data are presented as number (%)
AG atrophic gastritis, *IM* intestinal metaplasia, *OR* odds ratio, *CI* confidence interval

male sex, and education level, while the risk factors of intestinal metaplasia are *H. pylori* infection, old age, male sex, history of tobacco consumption, spicy food consumption, and family history of gastric cancer [5, 32]. It was hypothesized that improvements in atrophic gastritis and intestinal metaplasia after *H. pylori* eradication will be more likely among males than among females whose atrophic gastritis and intestinal metaplasia grades were lower, but sex was not a statistically significant factor. This finding might be related to fact that males more actively received eradication treatment and that among females, atrophic gastritis and intestinal metaplasia improved regardless of *H. pylori* infection [6]. A more definitive conclusion can be reached after further research from multiple perspectives.

8.4 Sex/Gender Differences in the *H. pylori*-Eradicated Population

Comparing the eradication trends in 2005, 2011, and 2016–2017 based on a national study that reported the *H. pylori*-positive rate and the eradication rate for 18 years, it was found that a history of eradication became more common in the older population, reflecting the trend for an increasing number of patients to receive eradication therapy in the 40–49, 50–59, 60–69, and above 70 age groups [3] (Fig. 8.4a). This trend could be explained by a greater interest in health with increasing age, which might be accelerated by health policies that actively promoted eradication by publicizing research results that found *H. pylori* infection promotes gastric cancer. Eradication in younger populations is desirable to prevent gastric cancer. It is not recommended to place an age limit on eradication therapy for the following reasons: (1) *H. pylori* eradication improves various indicators of the tumor microenvironment (e.g., *H. pylori* eradication reduced the proportion of patients with a pepsinogen I/II ratio of 3 or less, a biomarker of atrophic gastritis, in a group of patients with gastric cancer and dysplasia [conditions that are more common in the elderly] to the point that no significant difference was observed from a control group) [33]; (2) the survival rate of gastric cancer surgery patients after *H. pylori* eradication has recently increased [34]; and the average life expectancy in South Korea continues to increase. The eradication rates were 15.4%, 21.3%, and 26.7% among men in 2005, 2011, and 2016–2017, respectively, which were significantly higher than the corresponding rates of 12.2%, 16.8%, and 19.7% among women, suggesting more active eradication among men [3] (Fig. 8.4b). This finding can be interpreted as a result of more frequent health check-ups, more *H. pylori* tests conducted, and more exposure to information about the necessity of *H. pylori* eradication among men. Insurance coverage for *H. pylori* eradication in South Korea expanded in January 2018, and atrophic gastritis became a condition that prompts recommendation for eradication; therefore, eradication has recently become active in the private sector. In Japan, 600,000 individuals were treated with *H. pylori* eradication drugs annually, and after *H. pylori*-positive gastritis was covered by insurance in March 2014, the population that received eradication increased 2.3-fold to 1,400,000 [35]. Similarly, the proportion of the population receiving *H. pylori* eradication in South Korea is expected to increase further from the proportion of 23.5% in 2016–2017 [3].

8.5 Sex/Gender Differences in the Changes of Lipid Metabolism After *H. pylori* Infection

In 1969, Gallin et al. [36] found that the bacteria-induced systemic inflammatory response causes changes in lipid metabolism. Studies based on epidemiological research, such as various studies that examined the relationship between *H. pylori* infection and lipid metabolism, have been reported since. A study reported that among patients with coronary artery disease diagnosed by angiography, there were no changes in total cholesterol and low-density lipoprotein (LDL) cholesterol, but significantly lower HDL cholesterol levels, in *H. pylori* antibody-positive

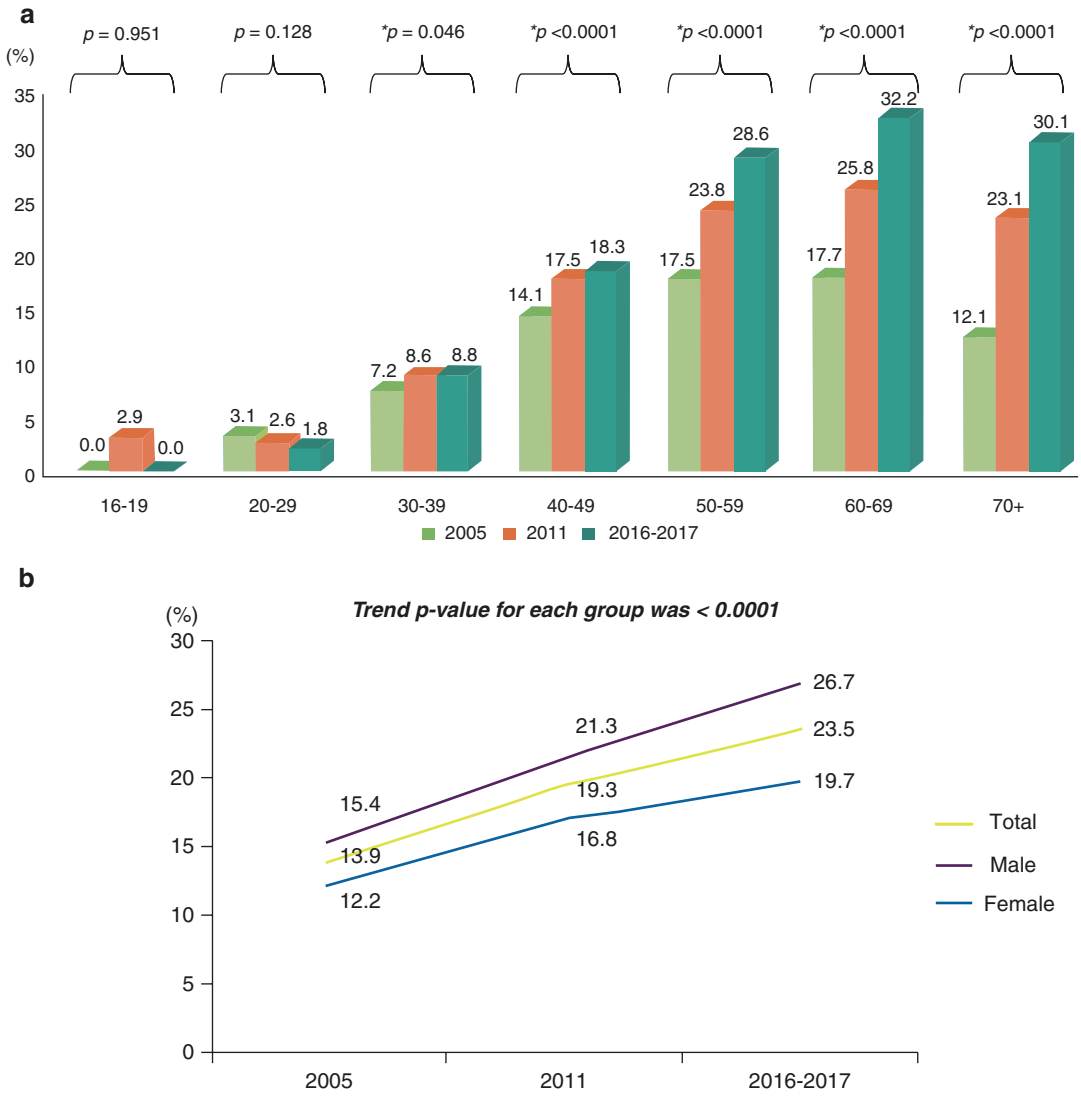

Fig. 8.4 Increase in the number of *H. pylori*-eradicated population in South Korea in 2005, 2011, and 2016–2017. (**a**) The rate of eradication increased rapidly with age. (**b**) When the *H. pylori*-eradicated population was compared by sex, the number was significantly higher among males than among females. *p value for trend (adapted from Lim et al. [3])

patients [37]. Another study reported that *H. pylori* infection was associated with higher triglyceride levels and lower HDL cholesterol levels [38], while a different study did not find such association [39]. A study of healthy adult males rather than patients found higher LDL cholesterol levels and lower HDL cholesterol levels in the *H. pylori* antibody-positive group than in the negative group [40]. A recent study in South Korea analyzing 15,195 participants in health check-ups reported that body mass index, waist circumference, total cholesterol, and LDL cholesterol levels were higher and HDL cholesterol levels were lower in the *H. pylori*-positive group than in the negative group [41]. Studies of the association between *H. pylori* infection status and lipid metabolism indicators are diverse in terms of their designs, samples, and results.

Summarizing studies that reported significant associations between *H. pylori* infection status and changes in lipid metabolism indicators, *H. pylori* infection is associated with higher levels of total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, and lower concentrations of HDL cholesterol and apolipoprotein A1 [37, 38, 40, 41]. These results are explained by the increase in the activity of lipoprotein lipase in adipose tissue and fatty acid synthesis and lipolysis in the liver caused by the increased release of cytokines related to *H. pylori* infection such as IL-1 or IL-6, IFN-α, and TNF-α [42, 43]. A study reported sex/gender differences in such changes [8]. A recent South Korean study of 1065 individuals reported that in the *H. pylori*-positive group (663, 62.3%), total cholesterol ($p = 0.003$), LDL ($p = 0.046$), and triglyceride ($p = 0.029$) levels were significantly higher, and HDL cholesterol levels were significantly lower ($p = 0.032$) [8]. In the multivariate analysis, males in the *H. pylori*-positive group had higher total cholesterol levels (OR 1.007; 95% CI, 1.002–1.011), while females had lower HDL cholesterol levels (OR 0.983; 95% CI, 0.968–0.998) [8]. This result is related to the reports that metabolic syndrome is more common in *H. pylori*-positive individuals, males, and older individuals [44] and that diabetes was more common only among males in the *H. pylori*-positive group, suggesting a relationship with sex hormones [45]. *H. pylori* infection affects lipid metabolism and diabetes incidence differently by sex/gender, and further studies are needed in this area.

8.6 Conclusions

H. pylori is transmitted at a young age when the immune system is not fully mature, and unless artificial eradication is attempted, the infection lasts for a lifetime. Sex/gender differences have been found in the epidemiology of *H. pylori*, chronic gastritis, the eradication rate, and lipid metabolism. There were no sex/gender differences in *H. pylori* infection until the age of 15 according to a 1998 study of the serum prevalence of *H. pylori* in all age groups conducted in South Korea, but the *H. pylori* infection rate among males become significantly higher than that among females after the age of 16. This phenomenon was observed in the 2016–2017 epidemiological survey as well. This finding cannot be explained completely by a cohort effect and indicates that *H. pylori* infections occur among males, who have higher exposure after the age of 15. Moreover, in a 2006 national multicenter study with 25,513 individuals, erosive gastritis, atrophic gastritis, and intestinal metaplasia were significantly more common among males than among females. The same result was found for atrophic gastritis and intestinal metaplasia in a 2011 national, multicenter study with 4023 participants of health check-ups. The prevalence of *H. pylori* infections is rapidly decreasing in South Korea. The histological findings of atrophic gastritis and intestinal metaplasia decreased among females from 2003 to 2018, but they did not decrease among males, indicating that tobacco consumption, alcohol consumption, and diet are important factors other than *H. pylori* infection contributing to the incidence of atrophic gastritis and intestinal metaplasia. The eradication rate of *H. pylori* is higher in older age groups, as older adults are more interested in maintaining health. The eradication rates were 15.4%, 21.3%, and 26.7% in 2005, 2011, and 2016–2017 among males, which were significantly higher than the corresponding rates of 12.2%, 16.8%, and 19.7% among females, suggesting active *H. pylori* eradication among males. A systemic inflammatory response to bacteria causes changes in lipid metabolism. Total cholesterol levels were higher in *H. pylori*-positive males, and HDL cholesterol levels were lower in *H. pylori*-positive females, indicating sex/gender differences in lipid metabolism post-*H. pylori* infection. Considering the differences in epidemiology, chronic gastritis, and lipid metabolism by sex/gender after *H. pylori* infection, tailored therapy including decisions about the timing of eradication therapy is recommended.

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Peptic Ulcer Disease

9

Nayoung Kim

9.1 Introduction

Peptic ulcers are caused by attacks on the stomach and duodenum by gastric acid and pepsin. Histologically, an ulcer occurs when a defect of the necrotic mucosa has progressed to below the muscularis mucosal layer, whereas erosion is defined as a defect limited to the mucosal layer. In the past, it was hypothesized that peptic ulcers occur when the aggressive factors of gastric acid and pepsin outweigh the defensive factors. Many studies have since clarified that *Helicobacter pylori* (*H. pylori*) infection and nonsteroidal anti-inflammatory drug (NSAID) use are important causal factors of peptic ulcers. The incidence of peptic ulcers peaked in 1910 according to Western data and gradually decreased from 1950 to 1980. Peptic ulcers were traditionally recognized twice as common among males than females, and duodenal ulcer (DU) was more common than gastric ulcer (GU). Due to the decreased prevalence of *H. pylori* and increased uptake of *H. pylori* eradication treatment, it was expected that the prevalence of peptic ulcers would decrease along with the decreased prevalence of *H. pylori* [1] (Fig. 9.1a). However, it was not. That is, according to 1995, 2000, and 2005 data, there were no changes in the prevalence of DU, but the prevalence of GU increased significantly [2] (Fig. 9.1b). This finding is interpreted as resulting from the increased number of patients with chronic diseases such as musculoskeletal or cardiovascular diseases as the population ages, resulting in the increased use of aspirin and other NSAIDs. Therefore, the incidence of peptic ulcers could differ by sex/gender if there is a disproportionate pattern in NSAID use according to gender. Summarizing studies on peptic ulcers published in South Korea from 1990 to 2007 [4], patients' age increased, the proportion of male patients and those with *H. pylori* decreased, and the proportion of bleeding increased from 17.8% in 1996–1997 [5] to 35.5% in 2007 [6] (Table 9.1) [4, 7, 8]. Reports from Western countries and Hong Kong have described a rising incidence of peptic ulcers among patients without identifiable causes of peptic ulcers such as *H. pylori* infection and NSAID use and have stated that mortality is high in this patient group [9]. When patients with peptic ulcers were followed up for 1 year after being classified according to *H. pylori* infection and NSAID use in South Korea, the rate of recurrence and direct fees associated with treatment were higher in peptic ulcer patients without known causes than patients with *H. pylori* infection or a history of NSAID use ($p = 0.002$) [10]. This result suggests that when peptic ulcers are discovered, *H. pylori* infection status and NSAID

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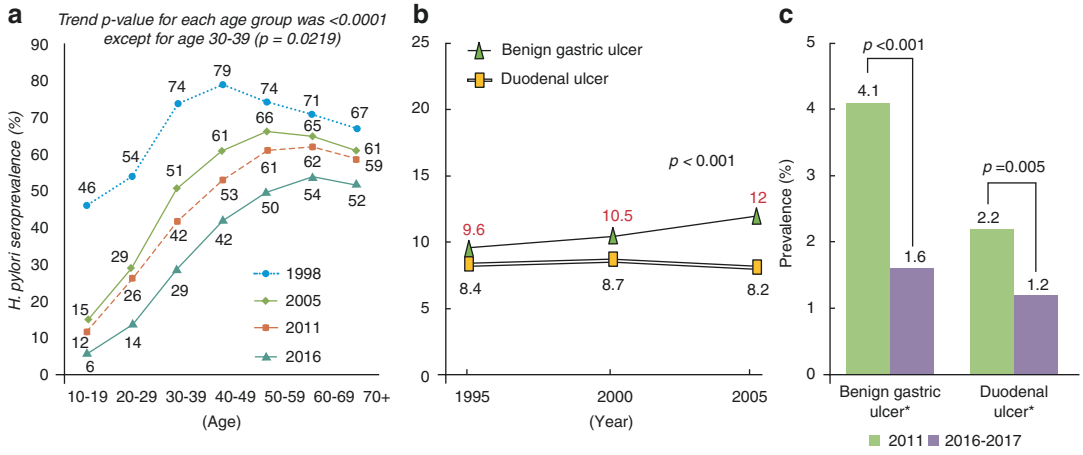

Fig. 9.1 Changes in the seroprevalence of *H. pylori* and the prevalence of peptic ulcers in 1995, 2000, and 2005. (**a**) The seroprevalence of *H. pylori* among individuals older than 16 and with no history of eradication therapy steadily decreased from 1998, 2005, and 2011 to 2016–2017 (*p for trend <0.05) (adapted from Lim et al. [1]). (**b**) According to the prevalence of peptic ulcers in 1995, 2000, and 2005, there were no changes in the prevalence of duodenal ulcers, but the prevalence of gastric ulcers increased (adapted from Kim et al. [2]). (**c**) The prevalence of gastric ulcers and duodenal ulcers was 4.1% and 2.2%, and the prevalence of gastric ulcers was higher than that of duodenal ulcers. In 2016–2017, the prevalence rates were 1.6% ($p < 0.001$) and 1.2% ($p = 0.005$), respectively, demonstrating significant reductions from 2011 (adapted from Nam et al. [3])

Table 9.1 Changes in the clinical characteristics of patients with duodenal ulcers in South Korea (adapted from Shim and Kim [4])

Year	1990 [7]	1995 [2]	1996 [7]	1996–1997 [5]	2000 [2]	2003–2008 [8]	2005 [2]	2006 [7]	2007 [6]
Number (*n*)	60	1518	80	180	1980	475	2042	61	310
Age (yr, mean ± SD)	47.8	–	50.8	53.8 ± 13.7	–	58.2 ± 14.9	–	58.1	61.5 ± 15.0
Aged patients (%)	–	–	–	32.2 (≥60 yr)	–	29.6 (>70 yr)	–	–	48.1 (>65 yr)
NSAID and ulcerogenic drugs[a] (%)	–	–	–	26.1	–	23.6 (NSAID), 22.5 (aspirin)	28.0	–	21.0
H. pylori infection (%)	–	–	68.1	82.8	59.7	72.6	57.2	–	48.0
Male (%)	82.6	–	75.4	77.2	–	70.3	–	66.7	66.7
Location of ulcer									
Gastric ulcer (%)	52.4	53.3	57.3	–	59.1	56.0	56.0	52.0	61.2
Duodenal ulcer (%)	40.4	46.7	44.4	–	40.9	44.0	44.0	40.7	38.8
Smoking (%)	–	–	–	58.9	–	34.3	–	–	–
Alcohol (%)	–	–	–	43.9	–	35.8	–	–	–
Bleeding (%)	–	–	–	17.8	–	–	–	–	35.5

NSAID nonsteroidal anti-inflammatory drug, *H. pylori Helicobacter pylori*
[a]Ulcerogenic drugs include aspirin, clopidogrel, warfarin

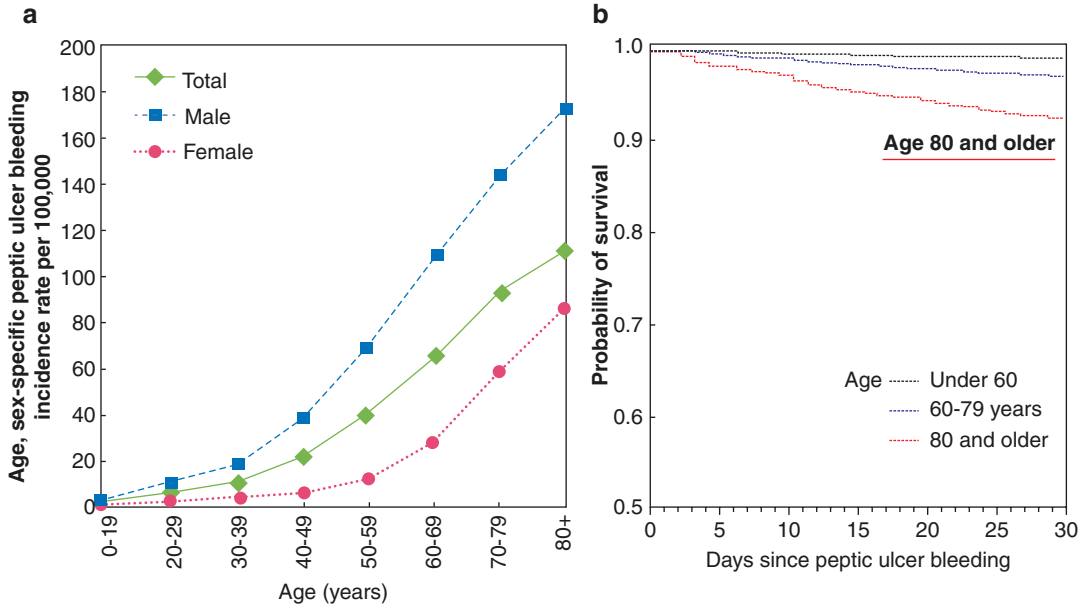

Fig. 9.2 Prevalence and mortality of peptic ulcer bleeding by age. (**a**) From 2006 to 2007 in South Korea, peptic ulcer bleeding among 21,107 individuals increased proportionately with age and was more than three times more prevalent among males. (**b**) Mortality within 30 days after peptic ulcer bleeding increased with age, especially dramatically in those aged 80 and older (adapted from Bae et al. [11])

use history should be elucidated first, and when the patient is negative for both, particular caution is needed. Bleeding [11] or perforation [12] due to peptic ulcers is more prevalent in older populations (Figs. 9.2a and 9.3a), and the associated mortality also increases dramatically in those older than 80 (Figs. 9.2b and 9.3b). The reason is that the defense mechanism of the gastric mucosa is damaged in the older population, making them vulnerable to damage by aspirin and other NSAIDs [13, 14]. Sex/gender differences in bleeding [11] and perforation [12] (Fig. 9.3a), which are complications of peptic ulcers, have been observed, with incidence rates higher in males than females for both. This sex/gender difference may be related to the female sex hormone estrogen, which increases the expression of tight junction proteins that close the gap between cells and reduce the mucosal permeability and bacterial movement [15]. This chapter describes the increasing incidence of peptic ulcers due to the aging population, even though the *H. pylori* infection rate has continued to decrease [1], and explores the disease mechanism of peptic ulcers involving NSAIDs, including aspirin, and sex/gender differences in the treatment and prevention of peptic ulcers.

9.2 Epidemiology and Sex/Gender Differences of Peptic Ulcers

Peptic ulcers display various symptoms ranging from asymptomatic cases to death from serious complications such as bleeding and perforation. Typical symptoms include epigastric discomfort, epigastric pain, heartburn, bloating, and loss of appetite, and other symptoms such as upper gastrointestinal (GI) bleeding and severe stomach pain and fever due to perforation can occur. However, the symptoms are not specific to the disease and not proportional to disease severity, so it is difficult to diagnose the condition based on symptoms alone. The final diagnosis is determined through endoscopy. DU decreased by 50%

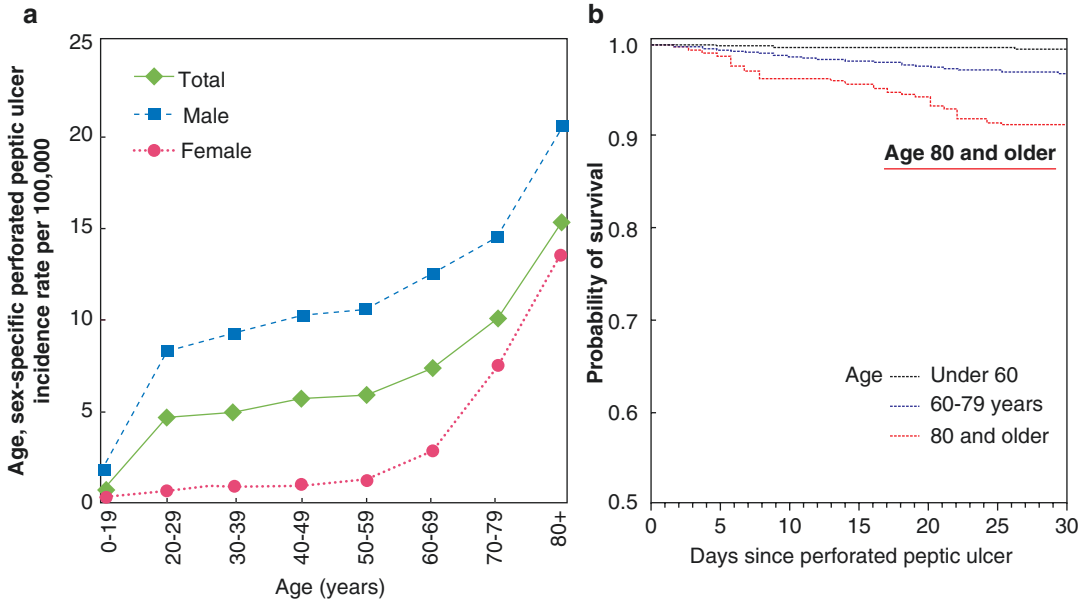

Fig. 9.3 Prevalence and mortality of perforated peptic ulcers by age. (**a**) From 2006 to 2007 in South Korea, perforation due to peptic ulcers among 4258 individuals increased proportionately with age and was around six times more prevalent among males. (**b**) Mortality within 30 days after a perforated peptic ulcer increased with age, especially dramatically in those aged 80 and older (adapted from Bae et al. [12])

from 1970 to 1985, and in the same time period, peptic ulcers decreased by 25%. Due to the increase of the older population, the decreasing trend has been less noticeable in recent years. According to a report on the incidence of peptic ulcers and their complications in South Korean tertiary hospitals in 1990, 1996, and 2006, the incidence of DU decreased, while the incidence of GU did not change or slightly increased [7]. The decreases in surgical treatment of ulcer bleeding (a complication of peptic ulcers) and in perforation suggest diminishing severity of peptic ulcers, which might be due to the prevention of disease progression through effective medical treatment [7]. Similarly, a study on the prevalence of peptic ulcers among 28,893 patients who visited gastroenterologists at 17 institutions in South Korea reported that the incidence of GU increased and the incidence of DU did not change from 1995 to 2000 and 2005, indicating that the overall incidence of peptic ulcers was gradually increasing [2] (Fig. 9.1b). NSAIDs are widely used to treat various acute and chronic musculoskeletal diseases, and the use of aspirin, which has anti-platelet properties, has recently become more frequent. Therefore, study results on epidemiological trends in peptic ulcers can depend on the proportion of the older population, who use NSAIDs more frequently in the sample, and the location of the study. In particular, it is important to assess whether a study is based on the diagnosis of peptic ulcers in hospital gastroenterology departments or in health check-up centers, which are similar to community-based studies. Thus, these results should be examined and interpreted separately.

9.2.1 Studies of Data from Health Check-Up Centers

Since an endoscopic diagnosis is necessary for peptic ulcers, it is difficult to conduct community-based studies. Studies of data obtained from health check-up centers are regarded as the closest to community-based studies. The largest study of the distribution of peptic ulcers included 25,536 individuals who received upper endoscopy examinations at 40 hospitals in South Korea from January to June 2006 and was conducted by

the Korean College of Helicobacter and Upper Gastrointestinal Research. The study reported the distribution of peptic ulcers [16] (Table 9.2). After excluding individuals who had a history of surgery related to disease in the digestive system or treatment for chronic diseases other than hypertension and diabetes, 59.5% of the 25,536 individuals were males (n = 15,180), and 40.5% were females (n = 10,356), making the sex ratio 1.5:1. The average age was 46.7 years, and the number of individuals in each age group was 1292 (5.0%) from age 16 to 29, 5684 (22.3%) in their 30s, 8885 (34.8%) in their 40s, 6126 (24.0%) in their 50s, 2936 (11.5%) in their 60s, and 613 (2.4%) over the age of 70 [16] (Table 9.2). In this sample population, 6.0% had used NSAIDs for more than one month. Subsequently, South Korea became an aging society, with more than 14% of the population aged 65 and above in 2018. Considering the increase in cardiovascular diseases, the proportion of the population that uses NSAIDs is expected to be higher. Among

Table 9.2 Prevalence of gastric ulcers and duodenal ulcers in 25,533 participants of national, multicenter health check-ups by sex, age, and area (adapted from Kim et al. [16])

Variable category	Number (%)	p-value
Benign gastric ulcer	Active stage:healing stage:scar stage:total	
Total (n = 25,533)	409 (1.7):423 (1.7):323 (1.3):1155 (4.5)	
Sex		<0.001
Male (n = 15,178)	318 (2.1):314 (2.1):243 (1.6):875 (5.8)	
Female (n = 10,355)	91 (0.9):109 (1.1):80 (0.8):280 (2.7)	
Age (years)		<0.001
16–39 (n = 6976)	70 (1.0):86 (1.2):31 (0.4):187 (2.7)	
40–59 (n = 14,328)	240 (1.7):243 (1.7):198 (1.4):681 (4.8)	
≥ 60 (n = 3548)	99 (2.8):94 (2.6):94 (2.6):287 (8.1)	
Area (province)		<0.001
Seoul (n = 9525)	98 (1.0):126 (1.3):111 (1.7):335 (3.5)	
Gyeonggi (n = 3085)	42 (1.4):45 (1.5):34 (1.1):121 (3.9)	
Kangwon (n = 1963)	13 (0.7):54 (2.8):27 (1.4):94 (4.8)	
Chungcheong (n = 3093)	26 (0.8):30 (1.0):32 (1.0):88 (2.8)	
Kyungsang (n = 3646)	133 (3.6):57 (1.6):66 (1.8):256 (7.0)	
Cholla (n = 3759)	96 (2.6):101 (2.7):47 (1.3):244 (6.5)	
Jeju (n = 462)	1 (0.2):10 (2.2):6 (1.3):17 (3.7)	
Duodenal ulcer	Active stage:healing stage:scar stage:total	
Total (n = 25,535)	243 (1.0):291 (1.1):1008 (3.9):1542 (6.0)	
Sex		<0.001
Male (n = 15,179)	196 (1.3):225 (1.5):757 (5.0):1178 (7.8)	
Female (n = 10,356)	47 (0.5):66 (0.6):251 (2.4):364 (3.5)	
Age (years)		0.075
16–39 (n = 6976)	77 (1.1):79 (1.1):259 (3.7):415 (5.9)	
40–59 (n = 15,011)	138 (0.9):185 (1.2):592 (3.9):915 (6.1)	
≥ 60 (n = 3548)	28 (0.8):27 (0.8):157 (4.4):212 (6.0)	
Area (province)		<0.001
Seoul (n = 9525)	71 (0.8):105 (1.1):487 (5.1):663 (7.0)	
Gyeonggi (n = 3085)	17 (0.6):42 (1.4):180 (5.8):239 (7.7)	
Kangwon (n = 1965)	11 (0.6):26 (1.3):40 (2.0):77 (5.9)	
Chungcheong (n = 3093)	21 (0.7):32 (1.0):113 (3.7):166 (5.4)	
Kyungsang (n = 3646)	59 (1.6):30 (0.8):110 (3.0):199 (5.4)	
Cholla (n = 3759)	62 (1.6):50 (1.3):49 (1.3):161 (4.3)	
Jeju (n = 462)	2 (0.4):6 (1.3):29 (6.3):37 (8.0)	

n number

the 25,533 participants in the 2006 study, 409 (1.7%), 423 (1.7%), and 323 (1.3%) were in the active phase, healing phase, and scarring phase of gastric ulcers, respectively, making up 1155 (4.5%) of the total sample. The proportions by sex were 5.8% and 2.7%, with a significantly higher prevalence in males ($p < 0.001$) [16] (Table 9.2). When stratified by age group, the prevalence was 2.7% in those from age 16 to 39, 4.8% in those from age 40 to 59, and 8.1% in those above the age of 60; the highest proportion was found in the 60 and above age group ($p < 0.001$), which may be related to the widespread use of NSAIDs [16]. Furthermore, 243 (1.0%), 291 (1.1%), and 1008 (3.9%) were in the active phase, healing phase, and scarring phase of DU, respectively, making up 1542 (6.0%). The prevalence was lower than that of GU for the active phase and the healing phase, but when the scarring phase was included, the total prevalence was higher than that of GU [16] (Table 9.2). The prevalence of DU in males and females was 7.8% and 3.5%, respectively, reflecting a significant difference ($p < 0.001$, Table 9.2). When stratified by age group, 5.9% were from age 16 to 39, 6.1% were from age 40 to 59, and 6.0% were over the age of 60. Unlike in GU, there were no significant differences by age in DU prevalence ($p < 0.075$) [16]. A subsequent study based on health check-up centers was a comparative study of peptic ulcers that included 4023 individuals from 2011 and 2504 individuals from 2016–2017 [3] (Fig. 9.1c). This study only analyzed the active and healing phases of peptic ulcers, excluding the scarring phase. The prevalence of GU and DU in 2011 was 4.1% and 2.2%, respectively, with a higher prevalence of GU [3] (Fig. 9.1c). In 2016–2017, the prevalence of GU and DU was 1.6% ($p < 0.001$) and 1.2% ($p = 0.005$), respectively, reflecting a significant decrease from 2011 [3] (Fig. 9.1c). The seroprevalence of *H. pylori* was an important risk factor for DU identified in a multivariate analysis of the risk factors of peptic ulcers ($p < 0.001$). The seroprevalence of *H. pylori* was 79.8% [17] in 2011, which significantly decreased to 51.3% in 2016–2017 ($p < 0.001$) [3]. The proportion of individuals who had undergone *H. pylori* eradication was 13.0% in 2011 [17], which increased to 17.5% in 2016–2017 ($p < 0.001$) [3], suggesting that the rapid reduction of *H. pylori* infection was the cause of the decrease in the prevalence of DU. The decrease in the prevalence of GU was not related to the decrease in the prevalence of *H. pylori*. Rather, it was suggested that the decrease in the prevalence of GU was due to reduced tobacco consumption, alcohol consumption, and history of NSAID use (more than once a week), as the prevalence of those risk factors was 21.9%, 61.8%, and 11.1% in 2011 [17] and 18.0%, 51.6%, and 9.7% in 2016–2017 [3].

9.2.2 Multicenter Studies of Data from Gastroenterology Departments at Tertiary Hospitals in 1995, 2000, and 2005

Large-scale studies (8441 participants in 1995, 10,350 participants in 2000, and 10,102 participants in 2005, 28,893 total) including individuals who received an endoscopy in tertiary hospitals in South Korea were conducted. During this period, the prevalence of peptic ulcers was 19.2% [2]. The prevalence of peptic ulcers increased from 18.0% in 1995 to 19.1% in 2000 and 20.2% in 2005 ($p < 0.001$). Patients with GU and patients with DU were different in terms of the impact of *H. pylori* and NSAID use [2]. In the past 10 years, the prevalence of *H. pylori* infection decreased significantly in South Korea ($p < 0.001$), but the *H. pylori* infection rate in the DU group was 65.4%, which was higher than the rate of 59.6% in the GU group [2]. Despite this decrease in the prevalence of *H. pylori*, the prevalence of DU did not change, with values of 8.4%, 8.7%, and 8.2% ($p = 0.449$) (Fig. 9.1b). Furthermore, GU increased, with prevalence rates of 9.6%, 10.5%, and 12.0% ($p < 0.001$) (Fig. 9.1b), indicating that the increase in NSAID use influenced the incidence of peptic ulcers more than changes in *H. pylori* infection [2]. Specifically, the prevalence of GU in the NSAID use group was 23.6%, which was markedly higher than that of 10.4% in the group without a history of NSAID use [2]. The

prevalence of DU in the NSAID use group was 12.3%, which was higher than 8.3% in the group without NSAID use history, but it was lower than that in the GU group [2]. The GU prevalence of 23.6% in the NSAID use group is similar to the findings of international reports that 15–30% of those who use NSAIDs experience peptic ulcers [18, 19]. In a report by Kim et al. that examined trends by year, GU increased in the NSAID use group from 17.6% to 19.4% and 28.0%, which are significantly higher rates ($p < 0.001$) than those of 7.5%, 9.2%, and 13.1% in the group that did not use NSAIDs [2]. The prevalence of duodenal ulcers was 11.2%, 9.8%, and 13.4% in the NSAID use group, which did not significantly differ from the prevalence of 7.9%, 7.6%, and 9.5% in the non-use group [2]. To summarize these findings, GU are highly influenced by the use of aspirin and other NSAIDs, while DU are strongly influenced by *H. pylori*. When these results are analyzed by age and sex, the prevalence of GU increased from 1995 to 2000 and 2005 proportionately to age, but the prevalence of DU instead decreased with age. Both types of ulcers were more prevalent in males—specifically, GUs were 2.25 times and DUs were 2.21 times more common among males than females [2].

9.2.3 Analysis of Peptic Ulcer Studies of Data from Gastroenterology Departments from 1990 to 2007

To summarize studies of peptic ulcers published in South Korea from 1990 to 2007 [2, 4–6, 8, 20] (Table 9.1), patients' age steadily increased, the proportions of male patients and those with *H. pylori* decreased, and the proportion of bleeding increased from 17.8% [7] in 1996–1997 to 35.5% [6] in 2007 [4] (Table 9.1). As the population ages, the prevalence of chronic musculoskeletal diseases, such as osteoarthritis, and cardiovascular diseases increases along with the use of NSAIDs, including aspirin. Damage of the GI mucosa increases in the older population, who are vulnerable to these analgesics, leading to predicted changes in the characteristics of patients with peptic ulcers. In fact, the average age of patients with peptic ulcers who were hospitalized at tertiary hospitals was 47.8 years [7] in 1990. The average age of 180 patients with peptic ulcers between 1996 and 1997 was 53.8 years [20], that of 475 patients with peptic ulcers from 2003 to 2008 was 58.2 years [21], and that of 310 patients with peptic ulcers in 2007 was 61.5 years [6], demonstrating an increasing trend [4] (Table 9.1). As *H. pylori* and NSAID use are the most important factors contributing to the development of these peptic ulcers, we evaluated their changes over time. The prevalence of *H. pylori* was 82.8% [20] in the peptic ulcer patient group from 1996 to 1997, 72.6% [21] in the patient group from 2003 to 2008, and 48.0% in the patient group in 2007 [6], displaying a rapid decrease (Table 9.1). In contrast, the proportion of patients who used ulcerogenic drugs, including NSAIDs, was 26.1% in 1996–1997, and the prevalence of NSAID use and aspirin use was 23.6% and 22.5%, respectively, marking a steep increase [4] (Table 9.1). An interesting fact is that the sex/gender ratio in peptic ulcer patients is changing remarkably. In 1990, 82.6% were males [7], but this proportion decreased to 66.7% in 2006 [7] and 2007 [6], indicating that peptic ulcers increased among female patients who started using NSAIDs more often [4] (Table 9.1). Theoretically, it may be expected that peptic ulcers due to NSAIDs can be ameliorated by the suspension of drugs, but it is difficult to discontinue NSAIDs due to their use for chronic diseases and chronic pain. In many cases, intractable peptic ulcers develop, leading to complications. Peptic ulcers in the older population are recognized as the most important side effect of aspirin and other NSAIDs [19, 22, 23].

9.3 Sex/Gender Differences in the Causes of Peptic Ulcers

In recent years, there is a higher proportion of the older population and people with underlying diseases such as diabetes, hypertension, stroke, and

cancer, and in this population, peptic ulcers without known causes such as *H. pylori* or aspirin/NSAID use are increasing [12, 24]. As such, peptic ulcers are classified into (1) peptic ulcers due to *H. pylori* infection, (2) peptic ulcers due to aspirin or other NSAID use, and (3) idiopathic peptic ulcers without either of the other two causes. Among these three categories, peptic ulcers due to aspirin or other NSAID use are more frequent in females and in the older population. This type of peptic ulcer is frequently accompanied by complications such as bleeding and perforation, and in patients with underlying diseases, it is associated with more than twofold higher mortality rate, although patients are often asymptomatic [7, 9, 25]. Asymptomatic cases of peptic ulcers due to NSAID use are relatively common because NSAIDs have an analgesic effect and exacerbate painless ulcers. Ultimately, the risk of complications such as bleeding and perforation increases. The elderly, who are less sensitive to pain and have weaker defense mechanisms, are more vulnerable to such complications. Bleeding is often observed in cases of peptic ulcers due to NSAID use because NSAIDs not only damage the gastric mucosal cells, but also suppress the synthesis of thromboxane A2 (TXA2) in platelets, thereby exerting an antiplatelet effect [4] (Fig. 9.4). Interest in patients with idiopathic peptic ulcers without *H. pylori* infections or a history of aspirin or other NSAID use is increasing, because the ulcer recurrence

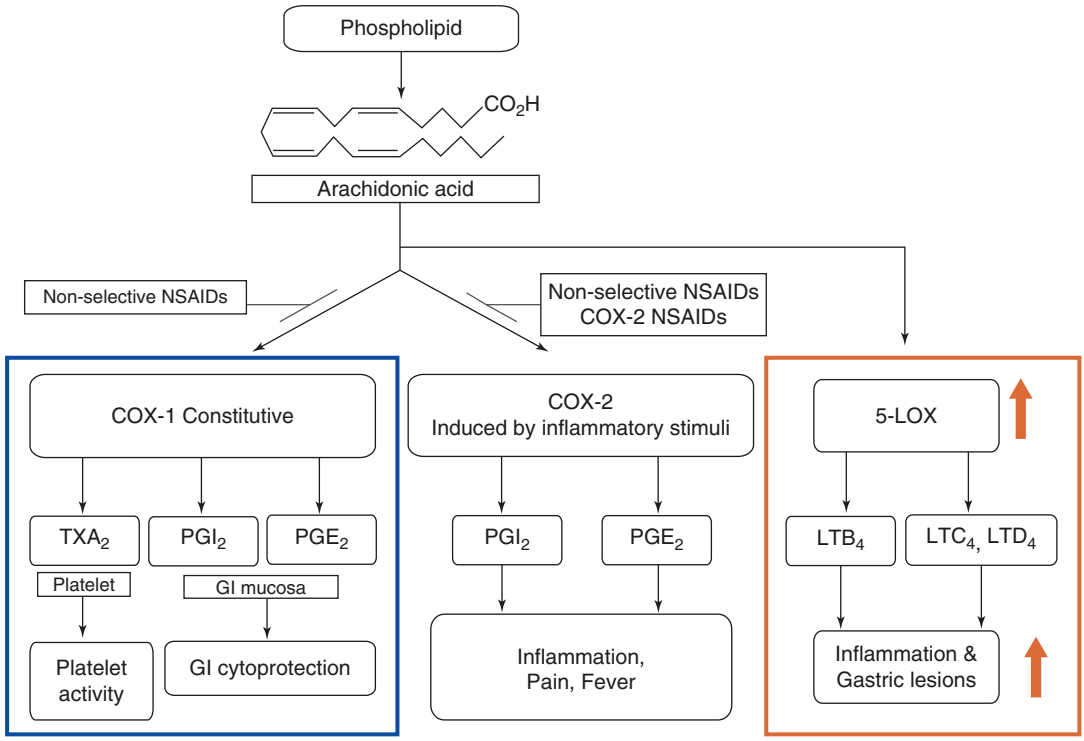

Fig. 9.4 Path changes of cyclooxygenase (COX) and lipoxygenase (LOX) due to NSAID. When an NSAID, including aspirin, is ingested, COX-1 decreases, thereby weakening the defense mechanism of the gastric mucosa, and thromboxane A1 (TXA2) decreases, reducing the hemostatic effect of platelets. COX-2, which increases during inflammation, also decreases. COX-2 selective NSAIDs have little effect on COX-1 and have the benefit of blocking only the COX-2 pathway. Non-selective NSAIDs block both COX-1 and COX-2, which activates the 5-LOX enzyme and increases the production of LTB4, C4, and D4, which are inflammatory factors. *COX* cyclooxygenase, *PG* prostaglandin, *TX* thromboxane, *LOX* lipoxygenase, *LT* leukotriene (adapted from Shim and Kim [4])

rates in these patients are high—at 35% in 2 years and 42% in 7 years—and the rates of complications and mortality are also high [3, 15, 16]. During a 5-year follow-up, the ulcer recurrence rates were 3.8% in patients with *H. pylori* infections, 10.9% in those with a history of NSAID and other medication use, and 24.3% in patients with idiopathic peptic ulcers, reflecting a significantly higher rate than those observed in the other two groups [26]. The prevalence of *H. pylori* infection was higher among males than among females, while a history of NSAID use was more common among females than males. Therefore, the sex/gender differences in these three types of peptic ulcers are briefly reviewed below.

9.3.1 Peptic Ulcers Due to *H. pylori*

The mechanism by which *H. pylori* infection causes DU is hypothesized to be either bacterial colonization in an area of gastric metaplasia that occurs in the duodenal mucosa, causing mucosal damage, or antral-predominant gastritis, increasing blood gastrin and stimulating gastric acid secretion to increase duodenal acidity and cause mucosal damage [27]. *H. pylori*-induced reductions in the secretion of bicarbonate in the duodenum are also known to be related to the incidence of ulcers. The suggested causes for GU are *H. pylori* bacterial colonization in both the gastric body and gastric antrum, normal or reduced secretion of gastric acid (unlike what occurs in DU), and reflux of duodenal digestive juice due to disorders in the gastric mucosal defense mechanism or pyloric sphincter [28]. As peptic ulcers occur in 5–10% of patients with *H. pylori* infection, factors related to the bacteria and the host and other factors beyond *H. pylori* infection are hypothesized to be relevant [28]. In the 1990s, the *H. pylori* infection rate among patients with DU was 94.2% [29], and that among patients with GU was 82.8% [20]. Both duodenal and gastric ulcers were twice as more common among males than females, suggesting the presence of sex/gender differences in host factors of peptic ulcers, such as tobacco and alcohol use, and in duodenal mucosa resistance.

9.3.2 Peptic Ulcers Due to NSAIDs

The main mechanisms through which NSAIDs damage the GI tract are the inhibition of prostaglandin (PG) synthesis due to systemic effects through the blood and direct effects on the GI mucosa. Overall, 10–60% of patients taking NSAIDs experience GI symptoms such as stomachache, heartburn, bloating, and indigestion [19, 22]. In fact, 10–20% of patients with rheumatoid arthritis who took NSAIDs for 6 months stopped medication due to GI symptoms [19, 23, 30]. According to a study that conducted upper GI endoscopy among patients who took NSAIDs, 10–40% of patients experienced GU within the first 3 months of NSAID use, and 4–15% experienced DU [18, 31–33]. The relative risk of upper GI bleeding among patients using NSAIDs is 3.8 [34], and the relative risk of death due to GI complications is around 4.2 [23]. Recently, daily intake of low-dose aspirin below 325 mg in order to prevent cardiovascular disease is increasing, and aspirin is being recognized as an important cause of peptic ulcers. Risk factors for GI complications in NSAID users are well-established through various case-control studies and cohort studies [19, 23], and the risk becomes clearer above the age of 50 when complications of ulcers are around 2–5 times more likely [35]. Other than old age, which is a factor that increases the risk of peptic ulcers due to NSAIDs, a history of peptic ulcers and combination of anticoagulants dramatically increase the risk of both peptic ulcers and GI bleeding [36]. The use of steroids on their own was not directly related to peptic ulcers, but when combined with NSAIDs, steroid use drastically increased the risk of peptic ulcers or complications of peptic ulcers. When a high NSAID dose is used, redundant use of NSAIDs, including aspirin, increases the risk of ulcers as well. A meta-analysis reported that the incidence of peptic ulcers was 3.5 times higher in patients who used NSAIDs and *H. pylori* infection [36]. The risk of ulcer bleeding was 1.79 times higher in patients with *H. pylori* infection, 4.85 times higher in those with NSAID use, and 6.13 times higher when both factors existed [37]. When NSAID use is required, patients should be tested

for *H. pylori* infection first and undergo eradication if positive. Gastric mucosal damage due to NSAIDs, including aspirin, can occur in various ways depending on the path through which the medication is absorbed (locally or through the bloodstream after being metabolized in the liver) [38–42]. Three important mechanisms include (1) increased membrane permeabilization, (2) suppression of cyclooxygenase (COX)-1 and PG formation, and (3) increased production of proinflammatory mediators [39]. Among these, the main pathophysiology of peptic ulcers due to repeated exposure to NSAIDs is the systemic effect of NSAIDs, which inhibit COX activity in the GI mucosa. Explanations of the three mechanisms follow.

9.3.2.1 Membrane Permeabilization

NSAIDs damage the GI mucosa through direct cytotoxic effects on gastric mucosal cells [43, 44], which are not related to COX inhibition [45]. When an NSAID is administered orally, it binds to hydrogen ions in the gastric juice, and the ionized NSAID penetrates the gastric cell membrane and enters gastric mucosal epithelial cells, causing intracellular acidification, inhibiting mitochondrial function, damaging the epithelial barrier [46], and causing necrosis and apoptosis of gastric mucosal cells [47]. This direct damage to the GI mucosa caused by aspirin or other NSAIDs is not believed to cause clinically important peptic ulcers. The evidence for this belief is that when enteric-coated aspirin is ingested, it is not dissolved in the stomach, which was expected to reduce gastric mucosal damage. However, compared to uncoated aspirin, enteric-coated aspirin did not reduce GI bleeding caused by peptic ulcers [48]. The fact that parenteral NSAIDs also cause GU and DU also supports this belief [49, 50].

9.3.2.2 COX-1 Inhibition and Decrease of Prostaglandins

NSAIDs cause clinically important GI mucosal damage through their systemic effects. The COX enzymes that play an important role in related mechanisms have two subtypes, COX-1 and COX-2, which have different functions [51]. COX-1 dissolves arachidonic acid to synthesize PG in the GI mucosa and produces TXA2 in platelets to help with bleeding [4] (Fig. 9.4). COX-1 synthesizes PG to protect the gastric mucosa from gastric acid, maintains the blood flow in the gastric mucosa, and produces bicarbonate [52, 53]. The absorbed NSAID suppresses activation of COX-1 to reduce endogenous PG synthesis. When PG synthesis is reduced, the gastric mucosa is damaged due to decreased secretion of mucus and bicarbonate from epithelial cells, reduced mucosal blood flow, decreased proliferation of epithelial cells, and reduced resistance to damage. Peptic ulcers due to NSAIDs are thus mainly caused by suppression of COX-1 production [54–56]. In contrast, COX-2 is activated by cell damage, endotoxins in conditions of disease, tumor necrosis factor-alpha (TNF-α), inflammatory mediators such as interleukin (IL)-1β, and tumor-derived factors [57, 58]. Considering that there are large differences in the production and function of COX-1 and COX-2, NSAIDs developed to suppress COX-2 only are known as selective COX-2 inhibitors. Unlike non-specific NSAIDs (ns-NSAIDs, such as indomethacin, naproxen, diclofenac, piroxicam, and ibuprofen), which can combine with both COX-1 receptors with small and sharp structures and COX-2 receptors with large and blunt structures, selective COX-2 inhibitors (celecoxib, etodolac, etc.) that can only combine with COX-2 receptors have been developed. Aspirin is categorized as an ns-NSAID and suppresses some COX-2-mediated reactions. Theoretically, selective COX-2 inhibitors can preserve the protective function of PG, mediated by COX-1, on the GI mucosa, but the dose of COX-2 inhibitors recommended for use in clinical practice can also suppress COX-1. As the possibility of damage in GI mucosa exists when only selective COX-2 inhibitors are used, caution is still needed [59, 60]. However, reports on celecoxib, a selective COX-2 inhibitor, have suggested that its risk of bleeding is lower than that of ns-NSAIDs [61, 62]. The Asia-Pacific guidelines on non-esophageal variceal bleeding categorize celecoxib separately from other NSAIDs as an NSAID with a lower possibility of bleeding [63].

9.3.2.3 Activation of Inflammatory Mediators

When the synthesis of PG is interrupted by an NSAID, the activation of lipoxygenase increases, producing leukotriene (LT), a product of the lipoxygenase pathway [64–66] (Fig. 9.4). Increased LT can cause inflammation, damage to the GI mucosa resulting tissue ischemia due to vascular endothelium spasm, and reperfusion stress, thereby increasing the production of reactive oxygen species (ROS) [64–66]. It also produces inflammatory mediators such as TNF-α, reducing the blood flow in the gastric mucosa, and damaging the GI mucosa by increasing the production of ROS [67].

9.3.3 Non-*H. pylori*, Non-NSAID Peptic Ulcers

Depending on the region, a wide range of prevalence of non-*H. pylori*, non-NSAID peptic ulcers has been reported. In South Korea, the prevalence is reported to be around 16.2–25.7% [10, 26, 68]. The inferred causes of ulcers in this patient group are excessive secretion of gastric acid, tobacco consumption, malignant tumors, other antiplatelet drugs (clopidogrel, ticlopidine, prasugrel, etc.), potassium chloride, bisphosphonate drugs, cytomegalovirus, herpes simplex virus infection, tuberculosis, syphilis, portal hypertension, Behçet disease, psychological stress, and other chronic comorbidities, but the exact causes are yet unknown [69–74].

The characteristics of idiopathic peptic ulcers without any certain causes are different from those of peptic ulcers that occur with *H. pylori* or a history of aspirin or other NSAID use. Among 173 peptic ulcer patients who were diagnosed through endoscopy at the Department of Gastroenterology at Seoul National University Bundang Hospital for 2 years from September 2006 to August 2008 and followed up for more than 1 year, when the idiopathic peptic ulcer group (n = 28, 16.2%) and the *H. pylori* or NSAID/aspirin peptic ulcer group (n = 145, 83.8%) were compared, no differences were found in age, sex, tobacco use, location of the ulcer, and bleeding [10]. The proportion of patients with a history of chronic diseases (hypertension, diabetes, heart disease, chronic kidney disease, etc.) in the idiopathic peptic ulcer group was 42.9%, which was higher than the 25.5% in the group with peptic ulcers due to *H. pylori* or aspirin or other NSAID use. However, the difference did not reach statistical significance (p = 0.062), which may have been due to the small number of study participants. An important difference is that the 1-year ulcer recurrence rate was 25.0%, which was significantly higher than the rate of 6.2% in the group with peptic ulcers due to *H. pylori* or aspirin or other NSAID use (p = 0.002) [10]. This finding demonstrates that treatment is easier in cases where the cause is definite such as *H. pylori* or NSAID/aspirin use. A report from Hong Kong also suggested the need to examine the cause of peptic ulcers since the mortality associated with bleeding due to idiopathic ulcers was higher [9].

9.4 Sex/Gender Differences in the Mechanism of Peptic Ulcers

The gastric epithelium is constantly attacked by endogenous harmful factors such as hydrochloric acid, pepsinogen/pepsin, and bile. Exogenous substances such as drugs, alcohol, and bacteria also constantly pass through the gastric epithelium. However, a very sophisticated biological system prevents damage in the mucosa and enables the repair of mucosal damage that occurs from time to time. Mucus, mucosal epithelial cells, blood circulation, and bicarbonate secretion are defensive factors. Even when offensive factors such as gastric acid and pepsin exert strong effects, adequate defensive function of the gastric and duodenal epithelium can prevent peptic ulcers caused by gastric and duodenal tissue damage. The mucosal defense system is composed of three levels: pre-epithelial, epithelial, and subepithelial factors. The first level of mucosal defense is the mucus-bicarbonate-phospholipid layer, which acts as a physicochemical barrier from various substances including hydrogen ion. Mucus secretion is controlled by the gastroduodenal epithelial cells.

Mucus is mostly composed of water (95%) and a mixture of phospholipids and glycoproteins (mucin). Mucous gel creates a non-stirred water layer that prevents the diffusion of molecules such as ions and pepsins. The secretion of bicarbonate is controlled by the gastroduodenal epithelial cells, and bicarbonate is secreted into the mucous gel to maintain the pH of the epithelial cell surface at 6 or 7 despite the pH inside stomach being strongly acidic, at a pH 1 or 2. The epithelial cells in the surface become the second defense barrier through factors such as the epithelial cell ionic transporter that produces mucus and maintains the intracellular pH, bicarbonate production, and intracellular tight junction-related proteins. The epithelial cells in the surface prevent protein denaturation and produce heat shock protein, which protects cells from factors such as increased temperature, cytotoxic substances, or oxidative stress. When the pre-epithelial defensive barrier is damaged, epithelial cells in the area migrate to repair the damaged area (restitution), and this process is not related to cell division. For effective restitution, the blood flow must be smooth, and the pH in the area must be alkaline. Restitution is controlled by growth factors such as epidermal growth factor (EGF), transforming growth factor (TGF)-α, and fibroblast growth factor (FGF). For large areas of damage that cannot be healed effectively through restitution, cell division must occur. Regeneration of epithelial cells is controlled by growth factors such as PG, EGF, and TGF-α. Along with the regeneration of epithelial cells, angiogenesis occurs in the damaged microvascular layer. FGF and vascular endothelial growth factor (VEGF) play important roles in the regeneration of blood vessels in the gastric mucosa. While peptic ulcers occur twice more frequently and bleeding and perforation are more common among males, the prevalence of peptic ulcers and complications is low among females. The reason for this was hypothesized to be related to estrogen, a female sex hormone. It was recently revealed that estrogen increased the expression of tight junction proteins, which close the gaps between cells and prevent mucosa permeability and bacterial migration [15]. In an animal study with rabbits, when an Ussing chamber experiment was conducted after injecting 17β-estradiol for 2 weeks and separating the esophagus, it was found that in the 17β-estradiol treatment group, there was a shorter distance between cells due to stimulants such as gastric acid through the augmentation of occludin [75]. Another mechanism is that estrogen promotes duodenal bicarbonate secretion, which was substantiated in both human [76] and mice [77] and thus has greater validity. As a brief introduction to these two studies, Tuo et al. analyzed epidemiological data to examine the incidence of duodenal ulcers by sex/gender and age, measured bicarbonate secretion in healthy individuals, and conducted immunoblot and immunohistochemical analysis to examine the expression of estrogen receptors (ER) [76]. The incidence of DU was significantly lower among females than among males. The incidence was 3.91–5.09 times lower among females before menopause (age 20–49) than among males of the same age, but in the 60 and above age group, the difference decreased, as the incidence among females was 1.32 times lower than that among males [76]. Basal and acid-stimulated bicarbonate secretion was higher among females aged 20–29 than among males, but this phenomenon was not observed in the 60–69 age group [76]. Moreover, females aged 20–29 had higher bicarbonate secretion than females aged 60–69, but this difference was not observed among males [76]. Serum estradiol levels were proportional to bicarbonate secretion according to the menstrual cycle before menopause, and it was explained that ER expressed in the duodenal plasma membrane and cytoplasm combined with estrogen to promote bicarbonate secretion and reduce the risk of DU among females [76]. A study based on experiments with mice aged 70–90 days reported that basal and acid-stimulated bicarbonate secretion was 1.5 times and 2.4 times higher, respectively, in female mice than in male mice [77]. This secretion disappeared immediately after administration of the ER antagonist ICI 182,780 or tamoxifen, increased rapidly after 17β-estradiol and an ERα agonist (1,3,5-Tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole), but was not related to progesterone [77]. In mice of both

sexes, 17β-estradiol stimulated bicarbonate secretion, but the secretion was 4.3 times higher in female mice than in male mice [77]. However, ER, ER mRNA, and ER proteins were expressed in the duodenal epithelial cells in mice of both sexes, and there were no sex differences in the degree of expression [77]. Furthermore, 17β-estradiol moved calcium into cells in the SCBN cell line; this cell line expresses ERα or ERβ, which was found to be related to cystic fibrosis transmembrane conductance regulator and Cl^-/HCO_3^- anion exchanger, suggesting a sex difference in the mechanism of DU [77]. An experiment was conducted on sex/gender differences in GU. The study compared the incidence of stress-related ulcers 2 weeks after distressing mice by tying their legs and putting them in a refrigerator for three hours. Stress-related ulcers occurred in 100% of male mice that were stressed, while ulcers occurred in 80% of female mice, indicating that males are more vulnerable to stress-related ulcers than females [78].

9.5 Changes in Peptic Ulcers in the Aging Population

According to a report by Statistics Korea about the population distribution by age in South Korea, the proportion of the population aged above 65 has been steadily increasing from 3.1% in 1970 to 12.2% in 2013. It is expected that the proportion will increase further to 24.3% in 2030 and 37.4% in 2050 (data from Statistics Korea). Kang et al. [14] found that as aging progresses, the lower third of the gastric mucosal layer is replaced with connective tissue along with the accumulation of various oxides; the production of mucus, bicarbonate, and PG is reduced; and vascularization is suppressed, reducing the resilience to mucosal damage in a study with mice of various ages [14]. As a mechanism of GI cellular aging, DNA damage was found in mucosal epithelial cells located close to the crypt and some neurons of the muscular layer plexus, and ROS increased in the muscular layer nerves [79, 80]. It is hypothesized that as aging progresses, neurons become more vulnerable to damage due to ROS [45]. Regarding the secretion of gastric acid, Majumdar et al. [81] explained that as aging progresses, secretion of gastrin in the gastric antrum decreases, resulting in reduced secretion of gastric acid, and the gastrin reactivity of gastric mucosa also decreases, limiting gastric acid secretion and growth promotion in the mucosa. Jo et al. [82] supported this finding by reporting a decreasing trend in gastric acid as aging progressed in an experiment with F344 mice. Meanwhile, a decrease in gastric acid secretion was not observed in healthy elderly individuals without atrophic gastritis [83], leading to some speculation that the decrease in gastric acid secretion in the older population is due to atrophic gastritis following *H. pylori* infection rather than aging itself [8].

9.6 Differences by Age and Sex/Gender in the Complications of Peptic Ulcers

Complications occur in around 25% of patients with peptic ulcers. The main complications are bleeding and perforation, and other complications include fistulas through penetration and obstruction of the gastric pylorus [84]. As hygiene improved and *H. pylori* infections decreased, the prevalence of peptic ulcers somewhat decreased, but the rate of hospitalization due to complications of peptic ulcers did not change much or even increased as NSAID use increased concomitantly with population aging [85, 86]. Peptic ulcer bleeding is the most common complication of peptic ulcers, occurring in 15–20% of patients with peptic ulcers [84, 87]. Although complications such as perforations or obstruction of the gastric pylorus are decreasing, peptic ulcer bleeding is increasing. The causes are hypothesized to be the increase in the use of NSAIDs, including aspirin, in the aging population and the lowered hemostatic effect of platelets as COX-1 and TXA2 in platelets are reduced as a result [4, 87] (Fig. 9.4). When the clinical features of patients with peptic ulcers diagnosed in the Seoul National University Bundang Hospital in 2007 were examined, peptic ulcer

bleeding was significantly more common in the older age group (60 and above) than in the younger age group (43.6% and 14.3%, $p = 0.035$), and the proportion of cases that required hemostasis therapy was 22.1% in the older age group, which was higher than the 13.7% in the younger age group ($p = 0.047$) [6]. The incidence of peptic ulcer bleeding among 48,400,000 individuals from 2006 to 2007 in Health Insurance Review and Assessment Service data was 22.1 per 100,000, and the 30-day mortality rate was 2.15% [11]. When analyzed by age, the 30-day mortality rate was 0.83% in the under 60 age group, which increased with age to 7.65% in the 80 and above age group [11] (Fig. 9.2a). The 30-day mortality rate was higher among women than among males [4, 11] (Table 9.3 and Fig. 9.2b). Gastroduodenal

Table 9.3 Comparison of the characteristics of 21,107 patients with peptic ulcer bleeding and 4258 patients with perforation in 2006–2007 National Health Insurance Service data (adapted from Shim and Kim [4])

	Peptic ulcer bleeding ($N = 21,107$) [11]			Perforated peptic perforation ($N = 4258$) [12]		
Variables	*n* (%)	30-day mortality No. of deaths (%)	Crude MRR (95% CI)	*n* (%)	30-day mortality No. of deaths (%)	Crude MRR (95% CI)
Total	21,107	454 (2.15)		4258	135 (3.17)	
Age (years)						
<60	11,099 (52.6)	92 (0.83)	1.00	3143 (73.8)	33 (1.05)	1.00
60–79	8453 (40.0)	243 (2.87)	3.50 (2.75–4.45)	892 (20.9)	59 (6.61)	2.76 (1.69–4.49)
≥80	1555 (7.4)	119 (7.65)	9.55 (7.28–12.5)	223 (5.2)	43 (19.28)	8.39 (4.81–14.1)
Sex						
Male	16,177 (76.6)	296 (1.83)	1.00	3650 (85.7)	74 (2.03)	1.00
Female	4930 (23.4)	158 (3.2)	1.78 (1.46–2.16)	608 (14.3)	61 (10.03)	1.71 (1.14–2.56)
Charlson comorbidity index						
Low (0)	19,779 (93.7)	366 (1.85)	1.00	3291 (77.3)	38 (1.15)	1.00
Medium (1–2)	1158 (5.5)	64 (5.49)	3.53 (2.75–4.53)	747 (17.5)	60 (8.03)	3.85 (2.46–6.03)
High (≥3)	170 (0.8)	14 (8.24)	4.62 (2.71–7.88)	220 (5.2)	37 (16.82)	8.52 (5.1–14.31)
PU-related hospitalization						
No	20,230 (95.8)	427 (2.11)	1.00	4053 (95.2)	118 (2.91)	Excluded[c]
Yes	877 (4.2)	27 (3.08)	1.47 (0.99–2.19)	205 (4.8)	17 (8.29)	
Ulcer-related drug[a] users						
No	15,605 (73.9)	301 (1.93)	1.00	2710 (63.6)	43 (1.58)	Excluded[c]
Yes	5502 (26.1)	153 (2.79)	1.45 (1.19–1.77)	1548 (36.4)	92 (5.94)	
Antiulcer drug[b] users						
No	8294 (39.3)	1.93[d]	1.00	3602 (84.6)	134 (3.72)	Excluded[c]
Yes	12,813 (60.7)	2.78[d]	1.45 (1.19–1.77)	656 (15.4)	1 (0.15)	

CI confidence interval, *MRR* mortality rate ratio, *PU* peptic ulcer, *PUB* peptic ulcer bleeding, *PPU* perforated peptic ulcer

30-day mortality has been calculated as the ratio of PUB and PPU-related deaths per 100,000 persons

[a]Ulcer-related drug has been defined as NSAIDs (including aspirin and COX-2 inhibitors), oral glucocorticoids, and anticoagulant (warfarin and clopidogrel)

[b]Antiulcer drug has been defined as proton pump inhibitors and H_2 receptor antagonist

[c]Excluded: due to statistical insignificance on stepwise logistic regression, as indicated by $p > 0.05$

[d]Original paper showed 30-day mortality (%) instead No. of deaths. The sum did not match with 454

perforation due to peptic ulcers occur in 2–10% of patients with peptic ulcers and was the most common cause of surgery due to peptic ulcers [88]. Perforation is a severe complication of peptic ulcers with a high mortality rate (25%). Peptic ulcer perforation is increasing in the older population due to the increased use of NSAIDs [67, 89, 90]. In South Korea, a study with 4258 patients with gastroduodenal perforation due to peptic ulcers that occurred from 2006 to 2007 reported that the incidence of perforation due to peptic ulcers was 4.4 per 100,000, the incidence among males (7.53) was 6 times that among females (1.24) (Fig. 9.3a), and the 30-day mortality increased with age [4, 12] (Table 9.3 and Fig. 9.3b). The mortality rate is so high in the older population due to delayed diagnoses because the symptoms of perforation might not be clear in older patients, patients who use steroids, immunosuppressants, or opioids, and patients with diabetes [91, 92]. An interesting fact is that bleeding and perforation, as complications of peptic ulcers, occur more frequently in males, but the mortality rate of such complications is higher among females. Estrogen acts as a defense mechanism, but in old age—around 20 years after menopause—the overall physical reserve mechanism that sustains life might be stronger in males than in females. A sex/gender difference in peptic ulcers could also be observed in the study of Kim et al., which was based on National Health Insurance claims data from 2006 to 2015 [93]. A total of 151,507 cases were hospitalized due to peptic ulcer bleeding, which was 34.98 per 100,000 person-years [93]. There were no changes from 2006 to 2008, but the incidence decreased 2.7% every year from 2008 to 2015 ($p < 0.05$) [93]. However, this decrease was only significant among males and not among females, which might have been due to the fact that NSAID use is more prevalent among women. The incidence of peptic ulcer bleeding was higher among males than females from age 40 to 70, but it was higher among females than males above the age of 80, suggesting that estrogen functions as a defensive mechanism before menopause [93].

9.7 Sex/Gender Differences in the Pharmacological Treatment of Peptic Ulcers

The aims of peptic ulcer treatment are alleviation of symptoms, improvement of the ulcers, and the prevention of ulcer-related complications and recurrence. When complications occur, endoscopic treatments or surgery might be required, but the foundation is pharmacological treatment. Little research has explored sex/gender differences in the treatment of peptic ulcers, but there is an interesting report that peptic ulcers occur more readily in stressed female mice than male mice and that the selective serotonin reuptake inhibitor fluoxetine did not improve female mice [78]. The authors caused ulcers by distressing 2–3-month-old, Sprague-Dawley strain mice by tying their feet and putting them in a refrigerator for 3 hours. Some mice were injected with 10 mg/kg of fluoxetine once in the stomach [78]. The stressed mice had reduced secretion of gastric acid and low gastric pH levels. Malonaldehyde (MDA) in the gastric tissue increased, but nitric oxide (NO)—an important factor related to catalase, which removes ROS, and mucosal defensive factors—decreased (especially in male mice) and gamma aminobutyric acid (GABA) in the brain cortex also decreased more in stressed male mice than female mice [78]. The antidepressant medication fluoxetine had an antiulcer effect in male mice, but no effect in female mice, suggesting that depression treatment may be effective in treating peptic ulcers in males [78].

For peptic ulcers caused by aspirin or other NSAIDs, whether the NSAID/aspirin can be stopped is an important question. Rheumatoid diseases are more common among females, and since females are more susceptible to pain, when they are taking multiple types of NSAIDs, it is not possible to discontinue the administration of those drugs. When individuals are hospitalized in long-term care hospitals for treatment, efforts to stop the administration of NSAID can be particularly difficult, so it is common for peptic ulcers due to NSAIDs not to be treated adequately. These intractable ulcers progress to bleeding or

perforation, but due to the pain-relieving properties of NSAIDs, symptoms do not occur, and the mortality among females is high. Therefore, when it is difficult to discontinue NSAIDs, a proton pump inhibitor (PPI) is suggested as the first-line treatment for peptic ulcers. When patients who have peptic ulcer bleeding require ongoing NSAID treatment, it is recommended for them to take a PPI with a selective COX-2-inhibiting NSAID [63].

H. pylori infection treatment is important for patients with peptic ulcers due to NSAIDs, since in such cases, peptic ulcer complications increase when *H. pylori* infection is present; in a multivariate analysis of the causes of peptic ulcer recurrence, *H. pylori* infection was found to be the only significant factor [21]. Therefore, *H. pylori* eradication is very important. However, some reports have stated that *H. pylori* infection is helpful for the treatment of ulcers since it increases the expression of COX-2 in the gastric mucosa and induces increased PG production, which is suppressed by NSAIDs [94, 95]. Thus, it is recommended to proceed with *H. pylori* eradication treatment after the treatment for GU is completed in case of GU due to NSAID/aspirin use [96].

9.8 Sex/Gender Differences That Should Be Considered for Peptic Ulcer Prevention Strategies

As the population ages and degenerative arthritis becomes more prevalent, NSAID use is increasing. In the United Kingdom, the number of prescriptions for anti-inflammation and pain relief is 17,000,000 every year [97], and the number is expected to double from 2000 to 2030 [98]. In order to prevent side effects in the upper digestive tract mucosa and peptic ulcers and their complications, which accompany the use of NSAIDs, NSAIDs that minimize the damage in GI mucosa should be selected and used at the minimum dose for a short period of time, PPI or PG analogues should be used in combination, COX-2 selective inhibitors should be used, and diagnosis and treatment of *H. pylori* infection should be considered [38, 99, 100]. According to many studies, using clopidogrel instead of aspirin for primary prevention of cardiovascular diseases, combining histamine H_2 receptor antagonists (H_2RAs) or sucralfate when NSAIDs continue to be used, and using enteric-coated aspirin or buffered aspirin were not effective in preventing peptic ulcers or the complications [38].

When aspirin or other NSAIDs are used, the foundation of peptic ulcer prevention strategy is that special caution should be taken for those aged above 65. In South Korean studies, examples of combining ulcer prevention drugs, including PPIs, with NSAID prescriptions are increasing. One European study reported that the proportion of prescriptions combining NSAID and ulcer prevention drugs increased from 5.1% in 1997 to 15.9% in 2002 [101]. In another study, the proportion of combined prescriptions increased from 10.4% in 1997 to 21.0% in 2005, and the yearly incidence rate of peptic ulcers decreased from 1.1 per 1000 in 1997 to 0.52 per 1000 in 2005, indicating the effectiveness of combined prescriptions [32].

PPIs are slightly less effective than misoprostol in preventing peptic ulcers due to NSAIDs, but it has fewer side effects such as diarrhea or stomach pain than misoprostol, making it easier to use on an ongoing basis [102, 103]. PPIs are also effective in both preventing new ulcers and reducing ulcer recurrence in patients continuing to use NSAIDs [21, 104]. A study in the United States reported that combined prescriptions of NSAIDs and PPIs increased from 6.7% in 1998 to 8.2% in 2002 [105]. A study with patients who were using NSAIDs for a long time showed that when a high dose of famotidine (40 mg, twice a day) was taken in combination, the incidence of GU and DU reduced, suggesting that H_2RAs may prevent peptic ulcers [87]. A South Korean study on peptic ulcers and ulcer prevention drugs showed that a history of NSAID use and the incidence of peptic ulcers were not statistically significantly associated when PPIs were used within 4 weeks ($p = 0.334$). When PPIs were not used within 4 weeks, the incidence of peptic ulcers was higher in the NSAID use group (63.4%) than

in the non-use group (41.4%) ($p < 0.001$) [21]. This trend was similar in patients with history of H_2RA use. When H_2RAs were used within 4 weeks, the difference in the incidence of peptic ulcers according to NSAID use was not clear ($p = 0.097$), but when H_2RAs were not used within 4 weeks, the incidence of peptic ulcers was higher in the NSAID use group (73.3%) than in the non-use group (52.2%) ($p < 0.001$) [78], demonstrating the preventive effect of PPIs and H_2RAs. However, sex/gender differences were not analyzed in these studies, so there were no tailored strategies according to sex/gender differences in establishing preventive strategies. However, in light of reports that estrogen has a large effect on the incidence of peptic ulcers, planning to conduct sex/gender-specific analyses in future studies will help in preparing clinical guidelines.

9.9 Conclusions

Peptic ulcers are twice as common in males than in females. The incidence and prevalence of this condition are expected to decrease due to the use of PPIs, reduction in *H. pylori* infection, and increase in eradication. A study including participants of health check-ups reported such decreases, but a study of individuals who visited outpatient clinic of gastroenterology found that the prevalence of GU was increasing, as well as the proportion of female patients. Changes in GI mucosa, cardiovascular diseases, cerebrovascular diseases, and the increased use of aspirin and other NSAIDs for the treatment of chronic diseases including musculoskeletal diseases due to the aging population around the world are believed to be the causes for these trends. Symptoms can be non-specific in older patients, so complications such as bleeding and perforations commonly occur because peptic ulcers progress without being recognized. The incidence of bleeding and perforation is higher in males than in females, which is interpreted as resulting from the mechanism of estrogen, a female sex hormone, increasing the expression of tight junction proteins that seal the gaps between cells and reducing mucosal permeability, as well as the role of estrogen in promoting the secretion of a large amount of bicarbonate ions in the duodenal mucosa. However, the mortality of peptic ulcer bleeding and perforation is higher among females than in males, suggesting that older females who experienced menopause a long time ago are more vulnerable to the progression to severe illness, leading to death. Considering that the life expectancy of females is generally longer than that of males, this finding is very meaningful. Active research into sex/gender differences is necessary for tailored treatment in the future.

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10 Sex/Gender-Specific Medicine for Intestinal-Type and Diffuse-Type Gastric Cancer

Nayoung Kim

10.1 Introduction

Based on 2018 data, gastric cancer (GC) is the fifth most common cancer around the world, comprising 5.7% of all cancer incidence, and is the third deadliest cancer, accounting for 8.2% of total cancer mortality [1]. The incidence of GC is high in lower- and middle-income countries, and regionally in East Europe, East Asia, and Central and South America [2, 3]. The incidence of GC is particularly high in Asia, and approximately 75% of patients with GC are from Asia. In South Korea in particular, the incidence of GC is the highest in the world for both males and females [1, 4].

GC in South Korea is more common in males, with a male-to-female ratio of around 2:1 [5]. Clinically and pathologically, GC commonly occurs in older males. GC in males has a strong epidemiological association with *Helicobacter pylori* (*H. pylori*) infection and is more commonly the intestinal type. The Lauren classification, which has historically been the most widely used system of categorizing GC, divides GC into two types: the intestinal and diffuse types. These two types of GC demonstrate major differences in endoscopic presentation (Fig. 10.1a, b), histological findings (Fig. 10.1c, d), epidemiology, cause, and prognosis [6]. Intestinal-type cancer cells gather and grow into a mass, while diffuse-type cancer cells spread widely and grow into the gastric wall (Fig. 10.1e). Diffuse-type GC is more commonly found in females and in younger patients. *H. pylori* is more relevant for the diffuse type than for the intestinal type, but genetic factors have a stronger influence than environmental factors [2, 4, 7, 8]. In this chapter, cancer and estrogen/estrogen receptor (ER) and the sex/gender differences in GC are briefly reviewed.

10.2 Cancer and Estrogen

Estrogen is a steroid hormone that was first discovered as substance that controls the development and growth of human reproductive organs. It is now known that estrogen and ER take part in the physiological and pathological processes of cardiovascular, skeletal, and neuroendocrine systems beyond the reproductive system [7]. Estrogen exerts genomic and non-genomic effects through its receptors [9–11] (Fig. 10.2), which can be categorized into ERα and ERβ. With the discovery in 1996 of ERβ as a distinct receptor from ERα, which was discovered in 1958, new aspects of the effects of

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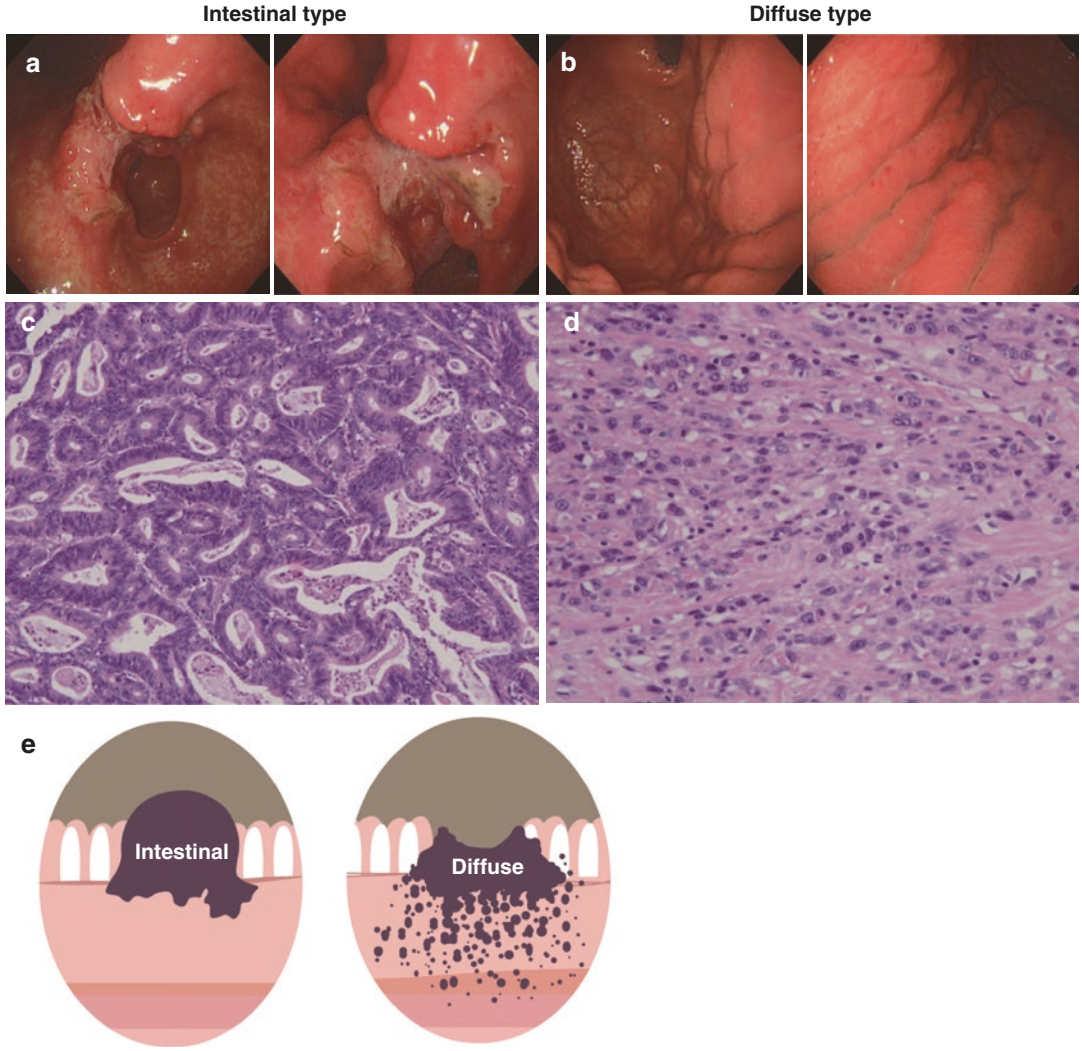

Fig. 10.1 Endoscopic findings (**a**, **b**), histological findings (**c**, **d**), and models of gastric cancer by histology (intestinal type and diffuse type) (**e**)

estrogen were revealed, enabling a wider range of related research [8]. ER belongs to the nuclear receptor superfamily [12], and variants other than ERα/ERβ continue to be discovered [13–15]. ERα is mostly distributed in the female reproductive organs such as the breasts, uterus, and ovaries, whereas ERβ is more widely distributed throughout various organs [16]. First, the role of estrogen/ER in the incidence of breast, endometrial, and ovarian cancers became known [17–19], and the fact that estrogen can have various effects on different organs is being revealed, as it was found that estrogen increases the risk of breast cancer [20] and endometrial cancer [21] while decreasing the risk of colon cancer [22]. As a result of continuing research on prostate cancer and colon cancer, targeted therapy drugs using estrogen increased the survival rates of these cancers and improved prognoses, but studies on the association between estrogen and GC are in their beginning stages.

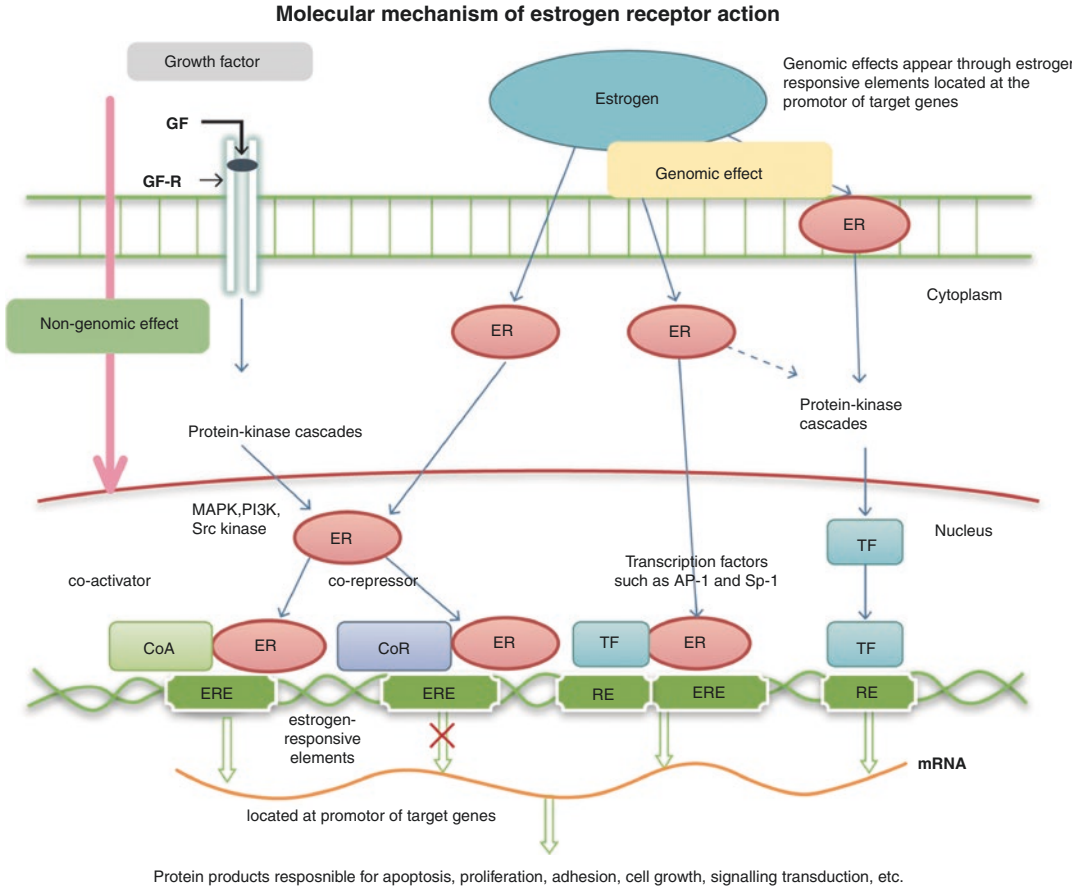

Fig. 10.2 Molecular mechanism of intracellular signaling of estrogen through estrogen receptors (ER). After estrogen combines with ER, it combines with the ligand-binding site of ER that exists in the nucleus to undergo morphological changes. It then becomes a ligand-ER complex, which combines with estrogen-responsive elements (EREs) in gene promoters. The receptors work with various co-activators or co-repressor multiprotein complexes that promote or suppress gene transcription. *ERE* estrogen-responsive elements, *RE* response element, *TF* transcription factor, *GF* growth factor, *CoA* co-activator, *CoR* co-repressor, *AP-1* activating protein-1, *Sp-1* stimulating protein-1 (adapted from Nie et al. [11])

10.2.1 Mechanism of Estrogen/Estrogen Receptor Related to Cancer

ER is found in the nucleus, cytoplasm, and cell membrane and is stimulated and activated by its ligands, thereby influencing gene transcription [11] (Fig. 10.2). The most typical mechanism is estrogen combining with the ligand-binding site of ER in the nucleus to undergo morphological changes and become a ligand-ER complex, which combines with estrogen-responsive elements (EREs) in gene promoters [11] (Fig. 10.2). The receptor then works with various co-activators or co-repressor multiprotein complexes that promote or suppress gene transcription [23]. To give a more detailed example of the mechanism of estrogen's effects on colon cancer, ERβ combined with estradiol (E2) interacts with EREs or transcription factors to directly control gene transcription [24]. Regarding non-genetic mechanisms, it has also been hypothesized that ERβ in colon cancer tissue plays an important role in suppressing the growth of colon cancer or the

progression of tumors through various intracellular actions such as induction of p53-mediated apoptosis, inhibition of the protein kinase C (PKC) signaling system to block cell cycle progression, or activation of intracellular calcium and cAMP pathways [24]. The ratio of ERβ and ERα determines the sub-pathways of estrogen, and they have transcription inhibition effects on each other. Therefore, the incidence of colon cancer among females is about half of that among males, the age of onset is 5–7 years later in females than in males, and colon cancer in females more commonly occurs in the right large intestine (ascending colon) [25]. For females, flat polyps (serrated adenomas) are commonly found on the right side and progress into cancer. The incidence of interval cancer (colon cancer that occurs in patients who received colonoscopy in the past 3–5 years) is higher in females, and the causes are hypothesized to be late detection of serrated adenomas in colonoscopies and the microsatellite instability (MSI) or CpG island methylator phenotype (CIMP) mechanisms, which progress faster than the chromosomal instability pathway (CIN pathway) [25]. In Europe, hormone replacement therapy was speculated to be a reason why colon cancer mortality was lower in females than in males and the survival rate was higher in females than in males from 1950 to 1990. The Women's Health Initiative showed that hormone replacement therapy in women after menopause decreased the risk of colon cancer by 56% ($p = 0.003$). According to a study conducted by the author's research team, in male azoxymethane/dextran sulfate sodium (AOM/DSS) inflammatory colon cancer mouse models, the incidence of colon cancer was high, and the incidence of colon cancer was significantly lower in male mice treated with estrogen [26]. It was also found that mice who underwent ovariectomy had a higher risk of right colon cancer than controls, displaying similar characteristics to those of colon cancer in human females [27]. However, studies with relevance to these issues have just started to be published regarding GC, and in-depth studies like those that can be found on colon cancer are still lacking. If the sex/gender differences observed in colon cancer are applied to GC, sex/gender is expected to be related to the histology and age of onset of GC, although more in-depth studies will be necessary moving forward.

10.2.2 Evidence That Sex/Gender Differences Should Be Reflected in Future Cancer Research

Sex differences in cancer may arise due to a combination of environmental, genetic, and epigenetic factors, as well as differences in gene regulation and expression. Extensive sex differences occur genome-wide and ultimately influence cancer biology and outcomes [28]. Despite their known importance in clinical medicine, differences based on sex/gender are among the least studied factors affecting cancer susceptibility, progression, survival, and therapeutic response. In particular, the molecular mechanisms driving sex differences are poorly understood and so most approaches to precision medicine use mutational or other genomic data to assign therapy without considering how the sex of the individual might influence therapeutic efficacy [28]. Thus, sex/gender-specific medicine is a promising area of cancer research. From the perspective of homeostasis between cancer stroma and organs, angiogenesis induced by sex hormones and the regulation of inflammation form an important foundation for understanding cancer progression in the two sexes/genders. Furthermore, as a systemic approach, cancer treatments based on immune checkpoint inhibitors are gaining prominence. For these treatments to become the core treatments for cancer types with a high frequency of genetic mutations, it would be helpful to understand how the immune system differs between the two sexes/genders. As it has been reported that the use of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors extend the survival of GC patients, studies on target groups that can benefit from immune checkpoint inhibitors are gaining attention. To increase the effectiveness of immune checkpoint inhibitors, comprehensive studies of the cancer tissue

immune system and sex hormones should be conducted.

Recently, the long non-coding RNAs (lncRNAs) have attracted increased attention of researchers in recent years. These lncRNAs measuring 10 kb or less in length which regulates transcription or post-transcriptional events provide very useful information that allows prediction of the degree of malignancy and a survival rate in cancer patients as clinically relevant biomarkers. Because symptoms and progression of cancer differ from onset to death between males and females, it is important to consider the gender of the patient when diagnosing cancer and predicting the progression [29]. The association between lncRNAs and sex hormones has been reported in common organs such as the lung, renal, and colon [29]. Although lncRNAs have not yet been widely used as definitive cancer indicators, recent studies have demonstrated the potential role of lncRNAs as biomarkers and therapeutic targets reflecting sex specificity in a number of different cancers including GC [29].

10.3 Incidence and Morality of Gastric Cancer

GC (cardia and non-cardia GC combined) remains an important cancer worldwide and is responsible for over 1,000,000 new cases in 2018 and an estimated 783,000 deaths (equating to 1 in every 12 deaths globally), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death [30]. Rates are twofold higher in males than in females. Incidence rates are markedly elevated in Eastern Asia (e.g., in Mongolia, Japan, and the South Korea [the country with the highest rates worldwide in both sexes]), whereas the rates in Northern America and Northern Europe are generally low and are equivalent to those seen across the African regions (Fig. 10.3). Several migrant studies have documented a strong environmental component in explaining the regional variation in GC incidence rates. GC incidence rates among first-generation Japanese migrants to Hawaii were observed to be lower than the rates among Japanese living in Japan, and the second-generation, Hawaiian-born Japanese experienced a further diminution in rates, although they still were higher than the rates among whites in the host population [31]. *H. pylori* is the main risk factor for stomach cancer, with almost 90% of new cases of non-cardia GC attributed to this bacterium [32, 33]. Although international variation in *H. pylori* prevalence correlates reasonably with that of GC incidence, factors other than *H. pylori* also are likely of major importance. There is a dietary component, with foods preserved by salting and low fruit intake increasing risk, and both alcohol consumption and active tobacco smoking are also established risk factors [34, 35]. Although they often are reported as a single entity, GC can generally be classified into two topographical categories. Rates of non-cardia GC (arising from more distal regions) have been steadily declining over the last one-half century in most populations [30]. The trends are attributed to the unplanned triumph of prevention [36] including a decreased prevalence of *H. pylori* and improvements in the preservation and storage of foods [30]. Cancers of the gastric cardia (arising in the area adjoining the esophageal-gastric junction) have epidemiological characteristics more similar to those of esophageal adenocarcinoma (EAC), and important risk factors include obesity and gastroesophageal reflux disease (GERD), with Barrett's esophagus (a condition resulting from GERD) also thought to increase risk; the incidence of these cancers has been increasing particularly in high-income countries [37].

10.4 Sex/Gender Differences in Gastric Cancer

To understand factors that explain the male predominance in GC, approaches from various perspectives are needed, and genetic factors related to the X/Y chromosomes, effects of differences in sex hormones, differences in health behaviors such as alcohol/tobacco consumption, *H. pylori* infection [38], and environmental factors in the tumor's surroundings (e.g., the gut microbiota) should be understood comprehensively. Among

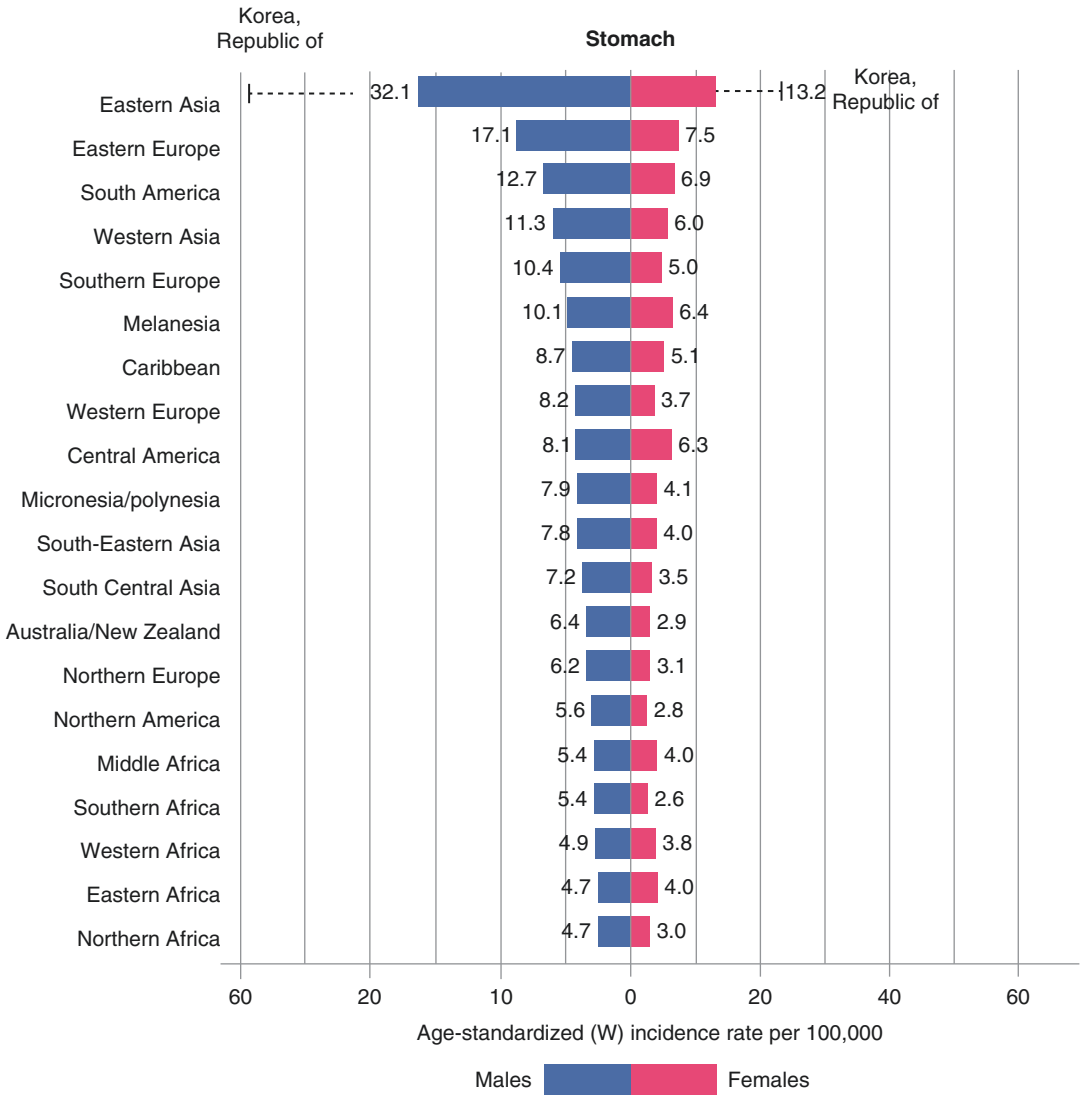

Fig. 10.3 Bar chart of region-specific incidence age-standardized rates by sex for cancers of the stomach in 2018. Rates are shown in descending order of the world (W) age-standardized rate among men, and the highest national rates among men and women are superimposed. Source: GLOBOCAN 2018 (adapted from Bray et al. [30])

the known risk factors of GC, *H. pylori* infection, alcohol consumption, and tobacco consumption are presumed to contribute to the male predominance, but these factors do not provide a conclusive explanation. Studies on the association between the incidence of GC and estrogen exposure [39, 40] are being published, but these findings still have yet to fully elucidate the sex/gender differences in GC incidence.

10.4.1 Differences in the Histology of Gastric Cancer by Sex/Gender and Age

A higher incidence of GC in males is observed consistently around the world, but not in all age groups [41–43]. Previous studies that examined the clinical pathology of GC by age group reported that younger patients with GC are more

likely to be female, have the diffuse or undifferentiated types histologically, and present with AGC. Older patients with GC are more likely to be male, have the intestinal type, and present with simultaneous tumors [44–46]. However, it is understood that even as overall environmental influences improve and the total number of GC patients decreases, a consistent proportion of diffuse-type GC will be maintained [47].

In a study that examined the age, menopausal status (pre-menopause or post-menopause measured at 5-year intervals), and histology among 758 patients with GC (531 males and 227 females) in Seoul Samsung Hospital from November 2014 to May 2021, female sex hormones were found to be a factor that inhibits the incidence of intestinal-type GC based on the finding that the diffuse type accounted for the majority of cases in females before menopause, while the proportion of the intestinal type becomes similar to that in males 10 years after menopause [48]. In addition, the ratio of intestinal- and diffuse-type GC in females became similar to that of male patients age of 70 or older, about 20 years after menopause [49] (Fig. 10.4). Another study reported the proportion of diffuse-type GC by age in three time periods (2003–2008, 2009–2012, and 2013–2018) among 1227 patients with GC who were diagnosed at Seoul National University Bundang Hospital in 16 years from 2003 to 2018 [50]. Throughout the entire study period, 62.7% of cases were early-stage GC, but this number increased in a statistically significant manner from 54.0% in 2003–2008 to 63.5% in 2009–2012 and 81.0% in 2013–2018 ($p < 0.001$) [50]. During the entire study period, the proportion of males was 66.7%, and the proportion of GC among female patients trended down from 33.8% to 29.7%, but the decreasing trend was not statistically significant [50]. The diffuse type according to the Lauren classification in females increased from 54.3% in 2003–2008 to 64.7% in 2013–2018, but the difference was not statistically significant [50] (Fig. 10.5a). The proportion of diffuse-type GC in the entire study period was 39.5%, and this proportion was especially high in younger patients, exceeding 90% in patients younger than 40. This finding was statistically significant in all three time periods ($p < 0.001$) [50] (Fig. 10.5b). According to a multivariate analysis of the risk factors for diffuse-type GC, female sex, age

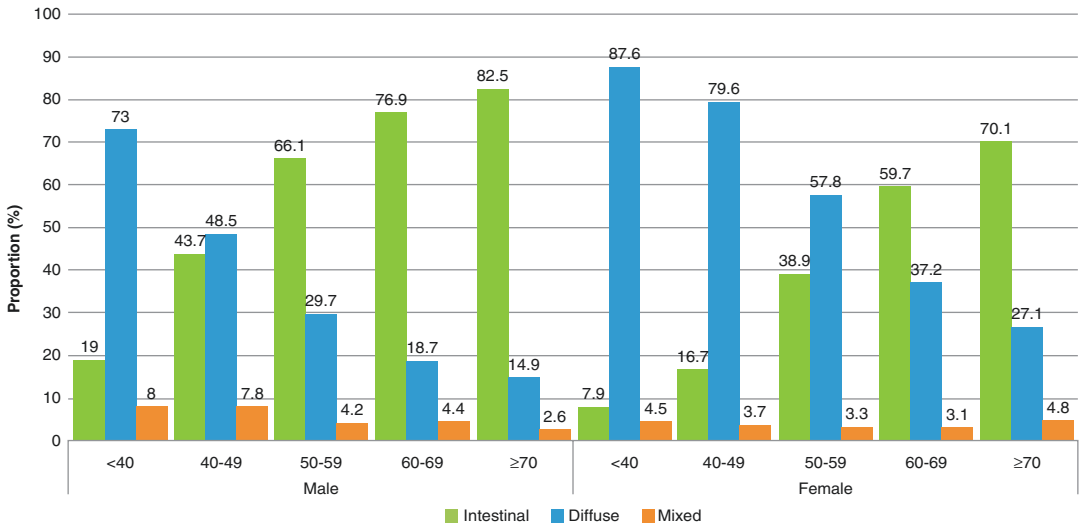

Fig. 10.4 Proportion of histological types of gastric cancer according to sex and age. The trend of increasing proportion of intestinal-type gastric cancers with age was observed in both males and females. In male patients, the proportion of intestinal-type gastric cancer increased steeply from age of 50 but in females, the proportion of diffuse-type gastric cancer remained high until 60 years of age. The ratio of intestinal- and diffuse-type gastric cancer in females became similar to that of male patients age of 70 or older, about 20 years after menopause

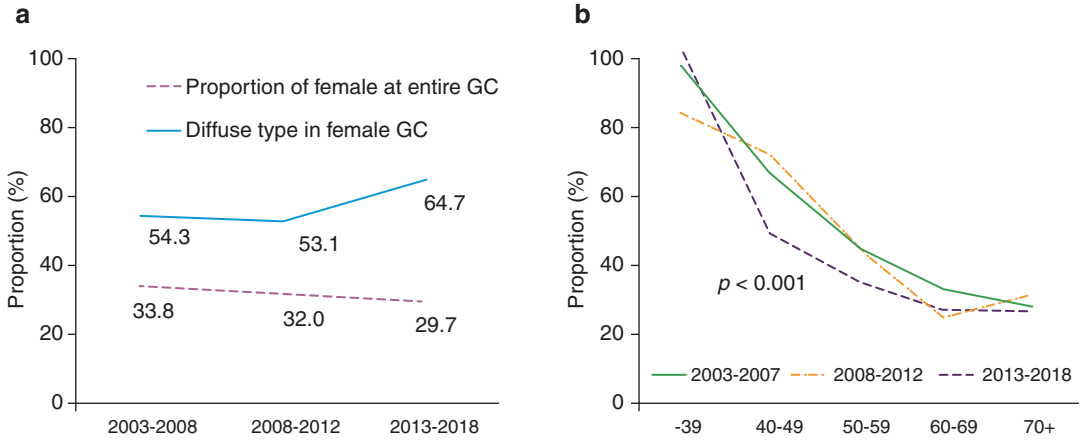

Fig. 10.5 Proportions of gastric cancer in females, of females with diffuse-type gastric cancer, and of diffusetype gastric cancer by age in three time periods: 2003–2008, 2009–2012, and 2013–2018. The proportion of females among the total number of gastric cancer cases changed from 33.8% to 29.7%, and the proportion of females with diffuse-type gastric cancer increased significantly from 54.3% to 64.7% (**a**). In all three time periods, the diffuse type accounted for more than 90% of cases in patients younger than 40 (**b**) (adapted from Lee et al. [50])

younger than 50, and AGC were independent risk factors, and a positive family history of GC and tobacco consumption was added in 2013–2018 [50] (Table 10.1). In another study, 88% of patients younger than 40 years old with GC had the diffuse type, among whom 35 (67.3%) were females and 17 (32.7%) were males. This finding was the opposite of the trend in patients older than 50, where the proportion of males was 65–70% [43]. The changes in the proportion of intestinal-type and diffuse-type cancers suggest that estrogen might have a protective effect on the intestinal-type GC [48, 51]. Thus, in young females, intestinal-type GC is much less than in males, and the percentage of intestinal-type GC increases over time after menopause, which is likely to be similar to males about 20 years after menopause, approximately at age of 70 [49].

10.4.2 Sex Hormones Such as Estrogen and Androgen and Their Receptors in Gastric Cancer

Four sex hormone receptors, estrogen receptor alpha (ERα), ERβ, progesterone receptor (PR), and androgen receptor (AR), were expressed independently and showed a decreased expression pattern in gastric tumors compared to adjacent normal tissues, suggesting that the sex hormone receptors may be partly involved in gastric carcinogenesis [52]. Several studies tried to explain sex difference of GC by investigating the role of ERs in GC. However, inconsistent results have been reported regarding ER expression in GC [7, 8, 38, 41, 53–56]; these inconsistencies may be due to differences in various experimental conditions, such as in vitro cancer cell line models, reagents, and protocols. Another reason could be the difference of ER such as ERα and ERß depending on the histology of GC. In patients with ER-positive GC, the frequency of undifferentiated GC is significantly higher than that of differentiated GC [38], and ensuing studies have also demonstrated an association between ER status and cancer stages in GC [39, 40]. Yi et al. showed that ERα expression was found to be associated with diffuse-type GC and shorter disease-free survival [41]. According to the previous studies, diffuse-type GC may be initiated by downregulation of E-cadherin by 17ß-estradiol (E2), the most potent isoform of estrogen, through ERα [57–59]. In contrast, well-differentiated gastric adenocarcinoma has a higher expression rate of ERß, and that poorly

Table 10.1 Multivariate analysis of diffuse-type gastric cancer (adapted from Lee et al. [50])

	2003–2007			2008–2012			2013–2018		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex									
Male	1			1			1		
Female	1.580	0.808–3.093	0.181	4.043	2.230–7.330	**<0.001**	4.072	1.253–13.226	**0.020**
Age									
<50	1			1			1		
50~69	0.214	0.117–0.391	**<0.001**	0.163	0.096–0.279	**<0.001**	0.354	0.153–0.818	**0.015**
≥70	0.092	0.044–0.195	**<0.001**	0.112	0.060–0.208	**<0.001**	0.125	0.042–0.376	**<0.001**
Cancer type									
EGC	1			1			1		
AGC	4.577	2.946–7.110	**<0.001**	4.325	2.778–6.735	**<0.001**	4.340	1.813–10.392	**<0.001**
H. pylori status									
Negative	1			1			1		
Positive	0.664	0.290–1.523	0.334	1.240	0.632–2.433	0.531	1.231	0.489–3.096	0.659
Family history of GC									
Negative	1			1			1		
Positive	0.742	0.433–1.271	0.277	1.266	0.782–2.050	0.338	0.420	0.179–0.989	**0.047**
Smoking status									
Never-drinker	1			1			1		
Ever-drinker	0.848	0.437–1.645	0.626	1.005	0.562–1.800	0.985	4.032	1.291–12.598	**0.016**
Alcohol consumption									
Never-drinker	1			1			1		
Ever-drinker	0.767	0.452–1.302	0.326	0.903	0.566–1.443	0.671	0.582	0.233–1.453	0.582

EGC early gastric cancer, *AGC* advanced gastric cancer, *GC* gastric cancer
Bold style means statistical significance

differentiated gastric adenocarcinoma is associated with a reduction or loss of ERß [60]. Recently there was an interesting study that suggested of the nuclear receptor estrogen-related receptor gamma (ESRRG) as a candidate factor influencing *H. pylori* infection-driven GC [61]. ESRRG suppressed *H. pylori* infection and cell growth induced by *H. pylori* infection in GC cells and organoid models [61]. In addition, *H. pylori* infection downregulates ESRRG expression [61]. Gene expression profiling revealed that trefoil factor 1 (TFF1), a well-known tumor suppressor in GC, is a downstream target of ESRRG [61]. Mechanistically, ESRRG directly binds to the TFF1 promoter and induces TFF1 gene expression [61]. Furthermore, TFF1 activation by ESRRG was inhibited by nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB)/p65, which is induced by inflammation, such as by *H. pylori* infection [61]. The author concluded that modulation of ESRRG-suppressing *H. pylori* infection could be a therapeutic target for the treatment of GC patients [61]. There is a possibility that ESRRG, a novel tumor suppressor, could be related with expression of ERß.

Several recent studies reported that the AR takes part in various pathways related to carcinogenesis in tissues other than the reproductive organs. Overexpression of AR appears to promote carcinogenesis and is related to lymph node metastasis and an adverse prognosis [43, 44]. Among patients whose neoplastic tissue of the stomach was positive for AR, AR did not show associations with other clinical and pathological factors but was independently associated with a low survival rate [42, 45, 46]. In recent studies, the stroma of intestinal-type GC in male patients was found to have a significantly higher positivity rate for AR than that in female patients, which might contribute to the higher permeability in male patients. This could be the reason of the greater invasiveness of this cancer type in males and presented the possibility of AR-targeted agents in GC treatment [62]. For instance, the males were more likely to develop tumor recurrence and liver metastasis than the females, especially in stage III GC, and the authors suggested that the cause was higher PD-L1 expression in males and GC patients aged 65 or older [63]. In addition, there are supporting data suggesting that sex hormones are the basis of these differences [64, 65].

Many studies are being conducted to explain the male dominance in GC, but significant biases still exist as the sex of animals is not differentiated in in vitro experiments and only 25% of GC cell lines are marked with sex. Because many clinical studies have not identified sex as a significant factor, data on factors related to the level of sex hormone exposure have not been collected. Some studies have examined the prognosis of GC based on the observed differences in clinical and pathological characteristics and histology by age and sex [66, 67], but even these studies introduced selection bias by limiting the type of treatment and most likely do not represent the entire population of patients with GC. Therefore, analyses using big data or prospective data will be appropriate to provide evidence for the hypothesis that there are sex/gender differences in the incidence of GC. For example, as a result of exploring the sex/gender differences in the large cohort of the Surveillance, Epidemiology, and End Results (SEER) database, which is a cancer patient registration program operated by the NCI through the US NIH, overall survival and cancer-specific survival among female patients with GC were found to be good [68].

10.4.3 Serum Pepsinogen II ≥ 20 μg/L and *H. pylori* Positivity Are Biomarkers for Early-Stage Diffuse-Type Gastric Cancer in Females Younger Than 40

Due to the non-specific symptoms of GC, many patients are diagnosed at advanced stages. A screening strategy is needed to identify GC in the early stages when the treatment possibility is high. In South Korea, the Korean National Cancer Screening Program for GC based on endoscopy and upper gastroenterography every 2 years for individuals older than 40 started in 2001 and greatly reduced cancer-related mortality [69].

However, the incidence of GC is 60 per 100,000 for males and 30 per 100,000 for females, so there are some issues in the effectiveness of conducting testing for everyone every 2 years. Gastroscopy is an invasive test that is avoided for individuals with an average level of risk. In Japan, gastroenterography has been used widely since it was difficult to meet the demand for endoscopy, but as individuals started to avoid exposure to radiation after the Fukushima Daiichi nuclear disaster, noninvasive mass screening using serum pepsinogen (sPG) has become more popular. Serum pepsinogen I (sPGI) and serum pepsinogen II (sPGII) are produced in different parts of the gastric mucosa [70]. sPGI is only secreted in the chief cells of the fundic glands, while sPGII is secreted not only in the fundic glands but also in the pyloric glands of the gastric antrum and duodenal mucosa. According to previous studies, low sPGI (<70 μg/L) and a low sPGI/sPGII ratio (<3) are markers of advanced atrophic gastritis, which is related to a high risk of GC [70, 71]. When *H. pylori* infection causes inflammation in the gastric mucosa, the production of sPGI initially increases and then decreases as the inflammation progresses to atrophic gastritis, while sPGII changes with a higher degree than sPGI [72], causing the sPGI/sPGII ratio to be reduced even further in advanced atrophic gastritis [73]. This standard can be applied to intestinal-type GC, which follows the Correa cascade, but it remains unclear whether it can be applied to diffuse-type GC, which has a different carcinogenic mechanism [74]. As the sPGI/sPGII ratio is low in atrophic gastritis, it is used as an effective biomarker of GC testing in Japan, but there are issues in using the standard cutoff used in Japan in GC testing in South Korea or other countries [75]. The low specificity of sPGI has also been pointed out as an issue [75]. The reason there are large differences in terms of the utility of pepsinogen biomarkers in Japan and in South Korea is that the predominant age of GC incidence is the late 60s in Japan, while it is the late 50s in South Korea. On average, patients with GC are 10 years younger in South Korea, and the proportion of diffuse-type GC is high (40%) in South Korea, whereas around 75% of cases of GC in Japan are intestinal-type GC [50, 75]. It has been reported that high-risk OLGA (operative link on gastric atrophy) and OLGIM (operative link on gastric intestinal metaplasia) stages are important predictive markers of both intestinal-type GC and some cases of diffuse-type GC [76], but a biomarker specific to diffuse-type GC would be very useful in South Korea. Some studies have reported an association between high titers of sPGII and diffuse-type GC [77–79], and the level of sPGII is known to be associated with the histological changes that reflect the level of inflammation in the gastric mucosa due to *H. pylori* infection. The level of sPGII was higher in patients with non-atrophic gastritis related to *H. pylori* and lower in those with atrophic gastritis, and the eradication of *H. pylori* reduced the level of sPGII to the level of the *H. pylori*-negative group [75, 80–83].

With this background, since sPGII is related to inflammation and elevated sPGII levels in the gastric mucosa and GC can be caused by estrogen or androgen depending on sex/gender differences and age, a study conducted a sex- and age-stratified analysis of these two variables (sPGII and *H. pylori* infection) [43]. The results showed that the presence of *H. pylori* infection and an sPGII level ≥20 μg/L were associated with diffuse-type GC, especially the incidence of early-stage diffuse-type GC [43] (Fig. 10.6 and Table 10.2). When the area under the curve (AUC) was calculated to confirm the utility of *H. pylori* infection and an sPGII level ≥20 μg/L as biomarkers for the prediction or diagnosis of early-stage diffuse-type GC, sensitivity and specificity were not significant for all GC (Fig. 10.6a) and all diffuse-type GC [43] (Fig. 10.6b). However, when patients with early-stage diffuse-type GC were stratified at age 40, *H. pylori* infection and an sPGII level ≥ 20 μg/L showed significantly more favorable diagnostic performance in the younger (age < 40) early-stage diffuse-type GC group (AUC 0.766, sensitivity 75.0%, specificity 74.2%, Fig. 10.6d) [43] than in the older (age ≥ 40) early-stage diffuse-type GC group (Fig. 10.6c). Moreover, among female patients younger than 40, early-stage diffuse-type GC could be diagnosed with very high sensitivity

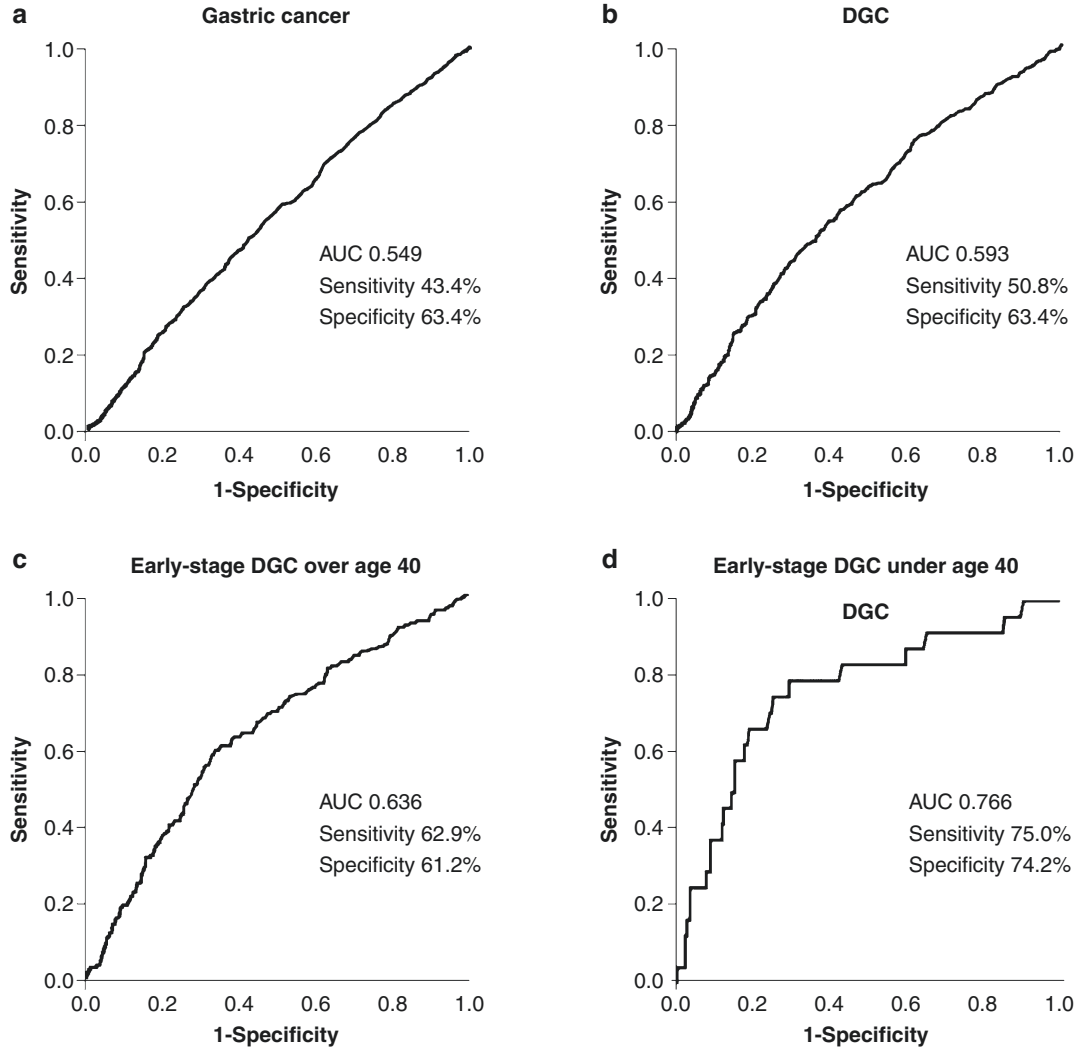

Fig. 10.6 Area under the curve (AUC) of *H. pylori* infection and serum pepsinogen II (sPGII) level of ≥20 μg/L. The sensitivity and specificity for all gastric cancer (**a**) and all DGC (**b**) were not significant, but when early-stage DGC patients were stratified at age 40, *H. pylori* infection and an sPGII level ≥20 μg/L showed significantly higher sensitivity and specificity in the younger (age < 40) early-stage DGC group (**d**) than in the older (age ≥ 40) early-stage DGC group (**c**). *DGC* diffuse-type gastric cancer (adapted from Baek et al. [43])

Table 10.2 Risk of early-stage diffuse-type gastric cancer by serum pepsinogen II levels and *H. pylori* infection status (adapted from Baek et al. [43])

Variable		Risk of early DGC (*p*-value)
Age < 40 years	sPGII <20 μg/L, *H. pylori* (−)	1
	sPGII ≥20 μg/L, *H. pylori* (+)	12.76 (0.001)
Female <40 years	sPGII <20 μg/L, *H. pylori* (−)	1
	sPGII ≥20 μg/L, *H. pylori* (+)	21.00 (0.006)

sPGII serum pepsinogen II, *DGC* diffuse-type gastric cancer

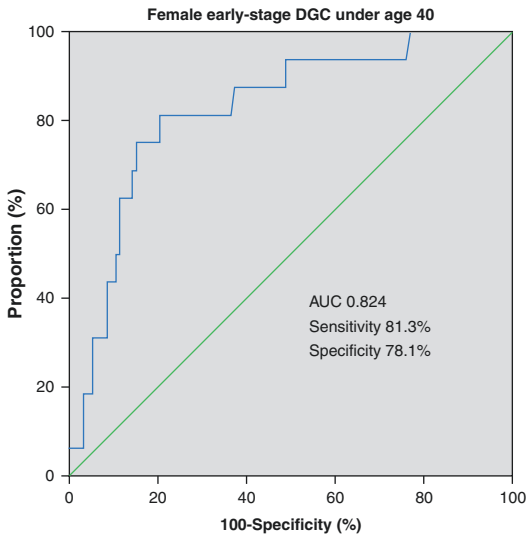

Fig. 10.7 Area under the curve (AUC) of *H. pylori* infection and serum pepsinogen II (sPGII) level of ≥20 μg/L among females under the age of 40 with early-stage DGC. *H. pylori* infection and an sPGII level ≥ 20 μg/L demonstrated high sensitivity and specificity for early-stage DGC in patients younger than 40. *DGC* diffuse-type gastric cancer (Modified from Baek et al. [43])

and specificity, with an odds ratio of 21 (AUC 0.824, sensitivity 81.3%, specificity 78.1%) [43] (Fig. 10.7). Additional studies are being conducted to examine whether these encouraging results support the use of these biomarkers in the national cancer management program.

10.5 Conclusions

GC is known to be more common in males than in females, at a 2:1 ratio, but 67.3% of patients with GC younger than 40 were found to be females [43]. This trend is the opposite of that found in GC patients over the age of 50, among whom males comprise 65–70%. Among females, the diffuse type accounts for most cases before menopause, but the proportion of the intestinal type becomes similar to that of males 10 years after menopause [48]. In summary, female sex hormones are related to the incidence of diffuse-type GC and inhibit the incidence of intestinal-type GC. Estrogen combines with the ER distributed in the nucleus, cytoplasm, and cell membrane and actively participates in various signaling systems to cause breast cancer, endometrial cancer, and ovarian cancer, while inhibiting colon cancer and liver cancer. Since gastroscopy is not actively recommended in individuals younger than 40, among whom GC is uncommon, and because the symptoms of GC are non-specific, the diagnosis of GC can be delayed. Among female patients younger than 40, the odds ratio of early-stage diffuse-type GC was 21 when they were *H. pylori*-positive and had an sPGII level ≥20 μg/L, indicating that these are important biomarkers for the diagnosis of early-stage diffuse-type GC, and additional studies are being conducted.

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11 Sex/Gender-Specific Medicine for Impact of Overweight, Obese, and Underweight on Gastric Cancer

Jieun Jang and Nayoung Kim

11.1 Introduction

As obesity incidence rate has increased noticeably for decades worldwide [1], interest in the impact of obesity on the development of noncommunicable diseases including cancers has increased [2]. Although it has been well established that excess body weight can increase the risk of several cancers including colorectal cancer, esophageal adenocarcinoma, kidney cancer, pancreatic cancer, and breast cancer [3–5] (Table 11.1), the association between obesity and gastric cancer (GC) has not been clarified yet. In addition, the association could be different according to anatomical location of GC, which is subdivided into cardia and non-cardia GC subtypes, with each GC subtype having its distinct pathological and etiological characteristics [6]. For this reason, when evaluating the impact of *Helicobacter pylori* (*H. pylori*) infection, a well-known carcinogen of GC, on GC development, the evaluation is limited to non-cardia GC in most cases [7]. The association of obesity with GC incidence also has different patterns depending on the anatomical location of the GC [8]. For patients with GC, it is well known that the risk of cardia GC is significantly elevated in the obese group than in the normal weight group, whereas non-cardia GC has been reported to have no significant association with obesity [8].

However, recent studies have revealed an increased GC risk in underweight population, especially in East Asia, where the incidence of non-cardia GC is the highest [9–12], and non-cardia GC accounts for more than 90% of overall GC incidence [13]. Additionally, GC is a male-dominant cancer with a male-to-female ratio of about 2:1 [14]. Meanwhile, it has been suggested that the association between obesity and the risk of GC might be different according to sex [8]. Hence, this review will discuss sex difference in the link between obesity and GC development and biological mechanisms involved in such difference in this chapter. In addition, the possibility of sex difference in the increased risk of non-cardia GC related to underweight, a new finding from recent studies, is discussed.

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Table 11.1 Relative risk of cancers associated with obesity (adapted from the World Cancer Research Fund/American Institute for Cancer Research [4] and Renehan et al. [5])

	Male		Female	
	Cancer type[a]	RR (95% CI)[b]	Cancer type[a]	RR (95% CI)[b]
Cancers with convincing evidence of increased cancer risk related to obesity	Colon cancer	1.24 (1.20–1.28)	Colon cancer	1.09 (1.05–1.13)
	Esophageal adenocarcinoma	1.52 (1.33–1.74)	Esophageal adenocarcinoma	1.51 (1.31–1.74)
	Kidney cancer	1.24 (1.15–1.34)	Kidney cancer	1.34 (1.25–1.43)
	Pancreatic cancer	1.07 (0.93–1.23)	Pancreatic cancer	1.12 (1.02–1.22)
	Thyroid cancer	1.33 (1.04–1.70)	Gallbladder cancer	1.59 (1.02–2.47)
			Endometrial cancer	1.59 (1.50–1.68)
Cancers with weak but possible evidence of an increased risk of cancer related to obesity	Leukemia	1.08 (1.02–1.14)	Leukemia	1.17 (1.04–1.32)
	Non-Hodgkin's lymphoma	1.06 (1.03–1.09)	Non-Hodgkin's lymphoma	1.07 (1.00–1.14)
	Malignant melanoma	1.17 (1.05–1.30)	Thyroid cancer	1.14 (1.06–1.23)
	Multiple myeloma	1.11 (1.05–1.18)	Postmenopausal breast cancer	1.12 (1.08–1.16)
	Rectal cancer	1.09 (1.06–1.12)	Premenopausal breast cancer[c]	1.16 (1.01–1.32)

RR relative risk, *CI* confidence interval
[a]Cancer type reported to be associated with obesity by the World Cancer Research Fund
[b]Relative risk of cancer incidence according to increase in body mass index of 5 kg/m^2 (Adapted from Renehan et al. [5])
[c]Only limited to Asia-Pacific female population

11.2 Association Between Overweight/Obesity and Gastric Cancer Incidence

As obesity incidence rate has increased noticeably for decades worldwide not only in males (Fig. 11.1a) but also in females [1] (Fig. 11.1b), interest in the impact of obesity on the development of non-communicable diseases has increased. Numerous studies have reported significant associations of obesity with type II diabetes, coronary heart disease, stroke, and several cancer types [15, 16]. Cardia GC, a malignant tumor located in the top inch of the stomach, is one of the cancers with a well-established relationship with obesity. Previous studies have found an increased risk of GC related to overweight or obesity [8, 17–23] (Table 11.2). The World Cancer Research Fund (WCRF) and International Agency for Research on Cancer (IARC) also consider overweight or obesity as a risk factor of cardia GC with sufficient evidences to support it [16, 24]. According to a recent systematic review that assessed the association between overweight/obesity and GC incidence, both overweight (body mass index [BMI] ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were significantly associated with elevated risk of cardia GC (hazard ratio [HR] 1.21; 95% confidence interval [CI], 1.03–1.42 for overweight; HR 1.82; 95% CI, 1.32–2.49 for obesity). In contrast, there was no significant difference in the risk of non-cardia GC between normal weight and obesity groups in the same study (HR 1.00; 95% CI, 0.87–1.15) [8]. Additionally, population attributable risk fraction of obesity on cardia GC incidence was estimated to be 8.8% among males (95% CI, 3.0–14.8%) and 11.2% (95% CI, 3.8–18.8%) among females. In other words, obesity accounts for about 10% of cardia GC in both males and females [25].

One of the mechanisms proposed to explain the relationship between obesity and the increased risk of cardia GC is the occurrence of gastroesophageal reflux disease (GERD) due to obesity [26–28] (Fig. 11.2). Since the increase in intra-abdominal pressure derived from abdominal obesity can cause reflux of gastric contents, the

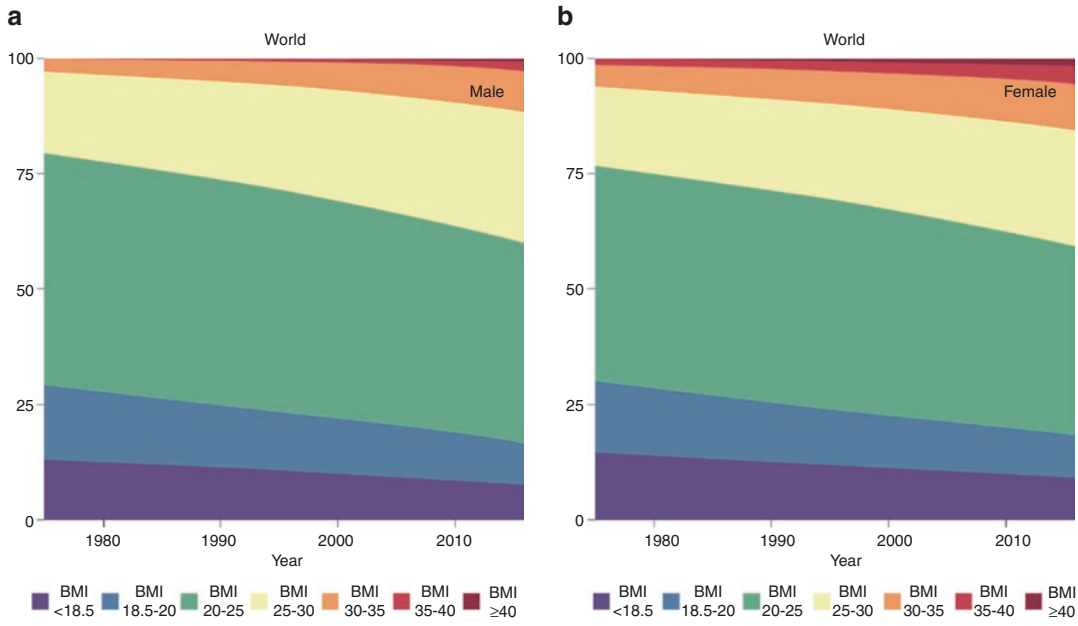

Fig. 11.1 Trends in the prevalence of underweight, overweight, and obesity worldwide (from 1975 to 2016): (**a**) male and (**b**) female (adapted from NCD Risk Factor Collaboration (NCD-RisC) [1])

incidence of GERD is estimated to be high in the obese group [29]. Several observational studies have confirmed the link between obesity and increased diagnosis and symptoms of GERD or esophagitis. Furthermore, a systematic review has also confirmed that overweight/obesity is significantly associated with the increase in GERD, although there is heterogeneity among studies (odds ratio [OR] 1.66; 95% CI, 1.61–1.71) [30].

Meanwhile, GERD is a spectrum disease that includes heterogeneous diseases with different clinical characteristics. Among these heterogeneous diseases, erosive esophagitis accompanied by damage to the esophageal mucosa has been reported to progress to Barrett's esophagus, a precursor of esophagogastric junction adenocarcinoma (about 1–13% of patients with erosive esophagitis) [31–33]. In short, obesity may increase the risk of cardia GC through a series of processes (from obesity to GERD to Barrett's esophagus to gastroesophageal junction adenocarcinoma).

In addition to physical mechanisms such as an increase in GERD due to abdominal obesity, several biological mechanisms including hyperinsulinemia and increase in insulin-like growth factors (IGFs) due to obesity have also been suggested. These biological conditions can promote cell division and cell survival while inhibiting apoptosis. Furthermore, it has been suggested that abnormal concentrations of various inflammatory cytokines such as adipokines (leptin and adiponectin), tumor necrosis factor-α (TNF- α), and interleukin-6 (IL-6) secreted from adipose tissues in obese and diabetic conditions can increase the risk of cancer development [34, 35].

11.3 Sex Difference in the Association Between Overweight/Obesity and Cardia Gastric Cancer Incidence

It has been evaluated whether there is a sex difference in the increase of GC risk derived from overweight and obesity. In a systematic literature review [8], the risk of GC in overweight or obesity group compared to normal weight was

Table 11.2 Reports on increased risk of cardia gastric cancer due to overweight and obesity

Author, year, country	Subjects number	*N* of cases	Sex	Follow-up period (year)	BMI measurement method	Confirmation of cancer	BMI (kg/m^2) category	RR[a] (95% CI)	RR[b] (95% CI)
Samanic et al., 2004, USA [17]	4,500,700	1049	M	12	Record at discharge	Cancer registration data	<30 ≥30	–	1.33 (1.05–1.68)
Lindblad et al., 2005, UK [18]	10,000 (controls)	195	M, F	7	Self-reported	Histological findings	<20 20–24 25–29 ≥30	1.37 (0.89–2.10)	1.46 (0.84–2.54)
Maclnnis et al., 2006, Australia [19]	41,528	30	M, F	6	Actual measurement	Cancer registration data	<25 25–29 ≥30	2.50 (0.80–7.60)	3.70 (1.10–12.40)
Samanic et al., 2006, Sweden [20]	362,552	121	M	19	Actual measurement	Cancer registration data	18.5–24.9 25–29.9 ≥30	1.16 (0.88–1.52)	1.09 (0.64–1.85)
Merry et al., 2007, Netherlands [21]	120,852	163	M, F	13.3	Self-reported	Cancer registration data	<20 20–24.9 25–29.9 ≥30	1.32 (0.94–1.85)	2.73 (1.56–4.79)
Corley et al., 2008, USA [22]	206,974	99	M, F	22.5	Actual measurement	Cancer registration data/medical record	18.5–24.9 25–29.9 ≥30	0.91 (0.55–1.53)	2.04 (0.99–4.21)
O'Doherty et al., 2012, USA [23]	480,475	191	M, F	9	Self-reported	Cancer registration data	18.5–24.9 25–29.9 30–34.9 ≥35	1.15 (0.80–1.65)	2.57 (1.82–3.64)
Stratification by sex									
Lindblad et al., 2005, UK [18]	10,000 (controls)	195	M, F	7	Self-reported	Histological findings	<20 20–24 25–29 ≥30	Male 1.41 (0.86–2.30) Female 1.20 (0.50–2.87)	Male 1.18 (0.58–2.42) Female 1.91 (0.76–4.84)

N number, *BMI* body mass index, *RR* relative risk, *CI* confidence interval, *M* male, *F* female

[a]Relative risk of cardia gastric cancer according to overweight (BMI of 25.0–29.9 kg/m^2)

[b]Relative risk of cardia gastric cancer according to obesity (BMI ≥ 30.0 kg/m^2)

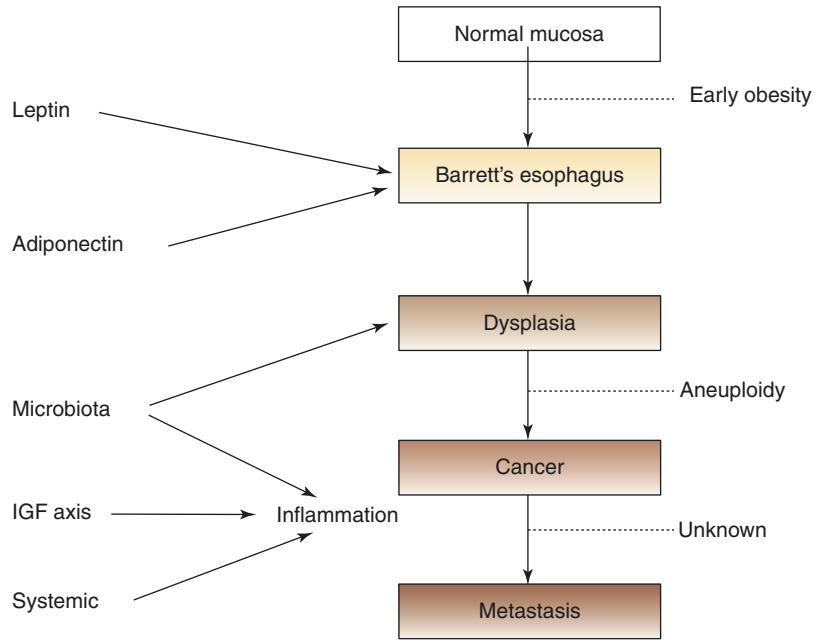

Fig. 11.2 Mechanism of gastroesophageal cancer incidence according to obesity. (adapted from Alemán et al. [28])

significantly elevated among males (HR 1.12; 95% CI, 1.00–1.24). However, there was no significant difference in GC risk between overweight/obesity and normal weight groups in females (HR 1.04; 95% CI, 0.93–1.16) [8].

A Korean report has shown that obesity is significantly associated with early-stage GC in males and that obesity is related to dysplasia (a precursor stage of GC) in females [36]. However, most of these results did not take into account the anatomical location of GC, making it hard to accurately evaluate whether there was a difference in the association between obesity and elevation in the risk of cardia GC according to sex.

Nonetheless, we can infer that obesity has an impact on the risk of cardia GC in males since previous studies have found significantly elevated risk of GC in males and reported that the positive association between obesity and GC is only limited to cardia GC [8].

As mentioned above, only a limited number of studies have evaluated the association between obesity and GC in consideration of both the anatomical location of cancer and sex concurrently. Therefore, it is difficult to clearly evaluate whether there is a sex difference in the extent to which obesity increases the risk of cardia GC. However, we can suggest the potential of sex difference in the link between obesity and cardia GC incidence based on several biological mechanisms.

Female hormone has been suggested as one of the major factors to explain the approximately two times higher incidence of GC in males than in females. Previous studies have reported a significantly lower risk of GC incidence in females who have a long fertility period, who have used hormone replacement therapy, and who have had a lot of childbirth [37, 38]. On the other hand, several studies have evaluated the difference in female hormone concentration according to the degree of obesity in females. These studies have found that BMI has positive correlation with concentrations of estrone, estradiol, and free estradiol in postmenopausal women [39–44]. When these study results are combined, the reason why the increase in the risk of GC associated with obesity is not found in females or the strength of the association is lower in females compared to that in males can be explained by high female hormone concentrations in obese females that can act as a preventive factor for GC

and offset the increased risk of GC due to obesity. In addition, a recent study has reported that obesity is associated with a significant increased risk of GC only in postmenopausal women, while there is no difference in GC risk according to BMI level in premenopausal women [45]. This result also supports the protective effect of female hormones against the increased risk of GC caused by obesity.

We can also infer the possibility of sex difference in association between cardia GC incidence and obesity from the difference in occurrence pattern of precursor lesion of cardia GC according to sex. A systematic review has shown that the prevalence of erosive esophagitis in males is 1.57 times higher (95% CI, 1.40–1.76) than in females. Erosive esophagitis has been suggested as a risk factor for Barrett's esophagus. Based on these results, we can explain the predominance of Barrett's esophagus in males than in females (male-to-female prevalence ratio: 1.71; 95% CI, 1.42–2.04) [46]. In Korea, it has been also reported that erosive esophagitis is 3.5 times more common in males than in females [47]. In addition, Barrett's esophagus and esophageal adenocarcinoma are more prevalent in males than in females [48].

Barrett's esophagus, which is more prevalent in males than in females and a precursor to gastroesophageal junction adenocarcinoma, has been suggested as a factor that can increase the risk of gastroesophageal junction adenocarcinoma [49]. Thus, there might be a sex difference in the level of increased risk of cardia GC due to obesity since males have a relatively higher risk of developing gastroesophageal junction adenocarcinoma precursor lesions derived from obesity compared to females.

Moreover, it has been reported that sex difference in the prevalence of GERD disappears in the older age group and that the prevalence of erosive esophagitis increases in women with menopause syndrome [50]. Therefore, difference in female hormone level between males and females might cause sex difference in the association between obesity and cardia GC.

In addition, it has been suggested that female estrogen plays a role in protecting the esophagus through reinforcement of esophageal tight junction protein, further supporting the potential of sex difference in the impact of obesity on cardia GC incidence [51].

On the other hand, it has been reported that obese patients have high concentrations of serum leptin. This serum leptin concentration has a positive correlation with the risk of Barrett's esophagus only in males [52]. Therefore, male dominance in the prevalence of erosive esophagitis and GERD including Barrett's esophagus due to obesity may cause a relatively higher risk of cardia GC in males than in females.

11.4 Association Between Underweight and Non-cardia Gastric Cancer Incidence

The increase in the risk of cardia GC due to obesity has been established through many observational studies, and a mechanism to explain this has been suggested. However, the impact of obesity on the incidence of non-cardia GC has not been clarified yet. A systematic review has shown no significant association between overweight/obesity and non-cardia GC incidence [8]. However, recent studies have reported that the risk of GC in the group with a low BMI is significantly higher than that in the group with normal weight, especially in East Asia [9–12, 53, 54] where non-cardia GC accounts for a high proportion of total GC incidence [13] (Table 11.3). These recent studies support the association between underweight and an increased risk of non-cardia GC.

The reason that previous studies could not find evidence for an increased risk of non-cardia GC in the underweight population might be because most of these studies have been performed on Westerners. The proportion of non-cardia GC in total GC is lower in Westerners than in Asians [13]. The prevalence of underweight and obese

Table 11.3 Reports on the increased gastric cancer risk in the underweight group and the decreased gastric cancer risk in the normal or overweight group

Author, year, country	Subjects number	Anatomical location	*N* of cases	Sex	Follow-up (year)	BMI measurement method	Confirmation of cancer	BMI (kg/m^2) category	RR (95% CI)	RR (95% CI)
Jang et al., 2019, Korea [11]	19,016	Non-cardia	485	M, W	12	Actual measurement	Cancer registration data	<18.5 18.5–22.9 23.0–24.9 25–29.9 ≥30	1.41 (0.92–2.17) <18.5 vs. 23.0–24.9 (kg/m^2)	1.38 (1.08–1.77) 18.5–22.9 vs. 23.0–24.9 (kg/m^2)
Jang et al., 2020, Korea, China, and Japan [12]	3544	Non-cardia	1591	M, W	2.4–7.6	Actual measurement or self-reported	Cancer registration data	<18.5 18.5–20.0 20.1–22.5 22.6–25.0 25.1–27.5 >27.5	1.59 (1.05–2.41) <18.5 vs. 22.6–25.0 (kg/m^2)	1.33 (1.01–1.76) 18.5–20.0 vs. 22.6–25.0 (kg/m^2)
Steffen et al., 2015, Europe [54]	391,456	Non-cardia	224	M, W	11.2	Actual measurement	Cancer registration data	Male Q1: 22.2 Q2: 24.5 Q3: 26.2 Q4: 28.0 Q5: 31.1 Female Q1: 20.5 Q2: 22.7 Q3: 24.6 Q4: 27.1 Q5: 31.6	0.61 (0.38–0.99) Q3 vs. Q1	–
Fan et al., 2017, China [9]	29,446	Non-cardia	626	M, W	19.8	Actual measurement	Clinical record	<20.32 20.32–21.75 21.76–23.30 ≥23.31	0.65 (0.51–0.83) ≥23.31 vs. <20.32 (kg/m^2)	0.86 (0.69–1.08) 21.76–23.30 vs. <20.32 (kg/m^2)
Bhaskaran et al., 2014, UK [53]	5,243,978	Stomach	3337	M, W	6	Actual measurement	Clinical record	<18.5 18.5–24.9 25–29.9 30–34.9 ≥35	1.42 (1.03–1.96) <18.5 vs. 18.5–24.9 (kg/m^2)	–

(continued)

Table 11.3 (continued)

Author, year, country	Subjects number	Anatomical location	*N* of cases	Sex	Follow-up (year)	BMI measurement method	Confirmation of cancer	BMI (kg/m^2) category	RR (95% CI)	RR (95% CI)
Stratification by sex										
Fan et al., 2017, China [9]	29,446	Non-cardia	626	M, W	19.8	Actual measurement	Clinical record	<20.32 20.32–21.75 21.76–23.30 ≥23.31	Male 0.59 (0.42–0.82) ≥23.31 vs. <20.32 (kg/m^2)	–
									Female 0.74 (0.51–1.08) ≥23.31 vs. <20.32 (kg/m^2)	–
Hirabayashi et al., 2019, Japan [10]	92,056	Distal ICD codes C16.2–16.6	2500	M, W	18	Self-reported	Cancer registration data	<19 19–22.9 23–24.9 25–26.9 ≥27	Male 0.94 (0.67–1.38) <19 vs. 23–24.9 (kg/m^2)	Male 1.00 (0.85–1.18) 19–22.9 vs. 23–24.9 (kg/m^2)
									Female 1.27 (0.76–2.14) <19 vs. 23–24.9 (kg/m^2)	Female 1.25 (0.95–1.66) 19–22.9 vs. 23–24.9 (kg/m^2)

N number, *BMI* body mass index, *RR* relative risk, *CI* confidence interval, *M* men, *W* women, *Q* quartile

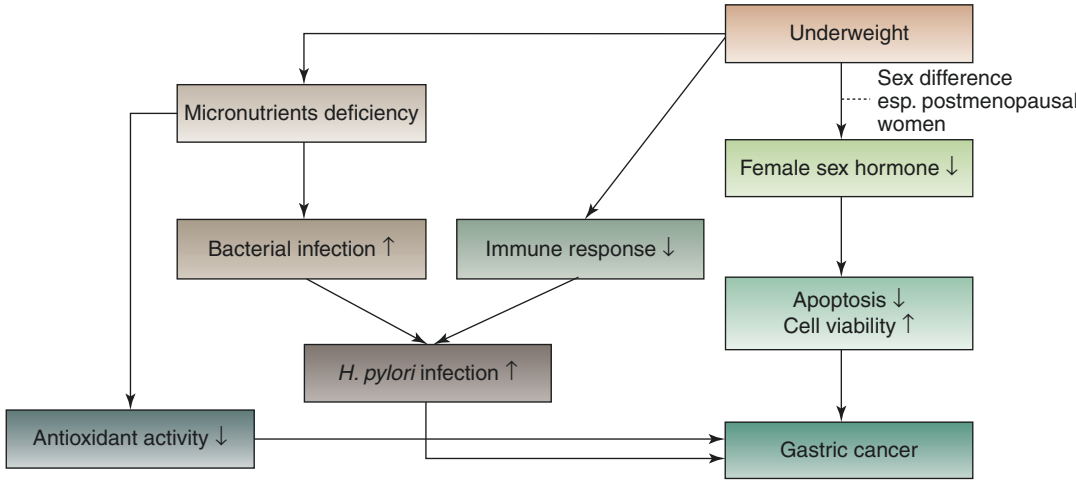

Fig. 11.3 Potential mechanisms on sex difference in the association between underweight and gastric cancer incidence and sex difference within this association

subjects are lower and higher in Westerners than in Asians, respectively [1]. Hence, it would have been difficult to observe an association between a low BMI and non-cardia GC incidence in previous studies based on Westerners. In addition, hypotheses tended to focus on the impact of overweight or obesity on the incidence of GC rather than the impact of underweight in previous studies. Therefore, the underweight group was excluded from analysis or combined with the normal weight group in most of previous studies, which might be limitations in evaluating the risk of GC associated with underweight in these studies.

Although the relationship between underweight and increased non-cardia GC risk has not been clearly established, several mechanisms can be considered to explain this relationship (Fig. 11.3). First, underweight is a form of malnutrition. Thus, underweight subjects might have deficiency of micronutrients [55]. It has been suggested that micronutrients can prevent cancer through antioxidant effects [56]. In addition, the underweight group might be more susceptible to infection [57] due to malnutrition with lower immunity [58]. Therefore, underweight may be an indicator reflecting the level of infection with *H. pylori*, a major carcinogen of non-cardia GC.

11.5 Sex Difference in the Association Between Underweight and Non-cardia Gastric Cancer Incidence

A limited number of studies have reported an increased risk of GC in the underweight group. These studies have been published relatively recently. Therefore, whether there is a difference in the association between underweight and GC risk between males and females has not been established yet.

Three observational studies have considered the sex difference among previous studies reporting an increase in GC risk related to underweight or a decrease in GC risk in the normal or overweight group [9, 10, 53]. One of these three studies was based on Westerners. It found that the degree of increase in the risk of GC due to underweight in males was lower than that in females [53]. However, there was no statistical significance in such sex difference. Another study was based on East Asians. It reported that the degree of increase in GC risk in the group with a BMI of 20.32–21.76 kg/m^2 compared to that in the group with a BMI of 23.31 kg/m^2 was similar between males and females [9]. In the third study, it was found that underweight was associated with an

increase in the risk of non-cardia GC only in females, although statistical significance was not found in that study [10]. Therefore, we could not obtain consistent conclusions on the sex difference in the relationship between underweight and GC incidence based on observational studies reported so far. However, the difference in the increased risk of GC by underweight between males and females could be inferred from a biological point of view.

It has been reported that concentrations of sex hormones including estradiol and estrone are significantly lower in postmenopausal women with a low BMI less than 22.5 kg/m^2 [59, 60].

On the other hand, high-dose estrogen therapy is related to a low standardized incidence of GC in a previous study [61]. Another study has found that diffuse-type GC, a more common histological type in females than in males, has a significant association with estrogen receptor positivity [62]. In addition to human studies, in vivo and in vitro studies on the protective effect of estrogen against GC have also been reported [63, 64].

Considering results of these studies above, estrogen concentrations in underweight females would be lower than those in normal and overweight females. As a result, the protective effect of female hormones against cancer development in females would differ according to BMI level. Therefore, underweight females might have a relatively higher risk of GC than normal and obese females.

11.6 Conclusions

GC is a male-dominant cancer. It is twice more common in males than in females. The increase in the risk of GC linked to overweight/obesity also differs between males and females. In this review, sex difference in the effect of obesity on GC incidence and mechanisms to explain such differences were discussed. In addition, recent reports on the increase in non-cardia GC risk associated with underweight and the possibility of sex difference in the association between GC incidence and underweight were considered. The elevated risk of cardia GC associated with overweight or obesity and the sex difference in this association might be attributed to the increase in female hormone concentration according to obesity and sex difference in the occurrence of cardia GC precancerous lesions. On the other hand, recent reports have suggested an increased non-cardia GC risk in underweight population as opposed to cardia GC affected by obesity. Most of these studies have been mainly reported in Asia with a high prevalence of non-cardia GC and *H. pylori* infection which is a major carcinogen of non-cardia GC. Thus, further studies are needed to determine whether the association between underweight and non-cardia GC is influenced by ethnicity or differences in levels of exposure to environmental factors such as eating habits, smoking, and alcohol depending on regions. In addition, we can assume that sex difference in the association between underweight and GC risk is caused by difference in female hormone concentration according to the level of body fat and sex, although this assumption needs to be evaluated in future studies.

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Part VI

Pancreas and Biliary Diseases

Pancreas and Biliary Diseases

12

Seon Mee Park

12.1 Introduction

Sex/gender differences of pancreas and biliary diseases could provide important and useful information to decide the diagnosis and treatment in clinical fields. Main causes of such sex/gender differences are estrogen and its related attributes. Environmental factors such as alcohol drinking, obesity, physical activity, and diets are also associated with such differences. The attitude for health facility utilization is also a contributor to different outcomes between genders. Because epidemiology and clinical characteristics of pancreas and biliary diseases are often different between Eastern and Western countries, gender differences need to be analyzed considering difference in ethnics, races, and countries. In this chapter, gender medicine about common diseases in the pancreas and the biliary tract will be summarized along with a literature review.

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12.2 Benign Diseases in the Biliary System

12.2.1 Gallstone Disease

12.2.1.1 Epidemiology

The prevalence of gallstones in adults has been reported to be 10–15% in Western countries and 5–10% in Asian countries [18]. In addition to such prevalence difference, the composition and sex preference of gallstones are also different between Western and Eastern countries. Cholesterol stones in Western countries constitute more than 80% of all gallstone cases, while proportions of cholesterol and pigment stones among gallstones are nearly matched in South Korea [22] or China [13]. Women show two to three times higher prevalence of gallstones than men in Western countries, while similar prevalence has been reported for both genders in Asian countries [13]. Females are dominant in the younger group (≤40 years old), while males are dominant in the older group (>50 years old) of gallstone diseases [23]. These differences are caused by cholesterol stone dominance in younger females, while pigment stones are dominant in older males [22] (Fig. 12.1). In addition, obesity (body mass index ≥25 kg/m^2), one of the risk factors of cholesterol stone, is slightly prevalent in women worldwide (male vs. female; 38.5% vs. 39.4% in 2015), while it is prevalent in men in South Korea (male vs. female; 42.3% vs. 26.4% in 2016) [6, 31].

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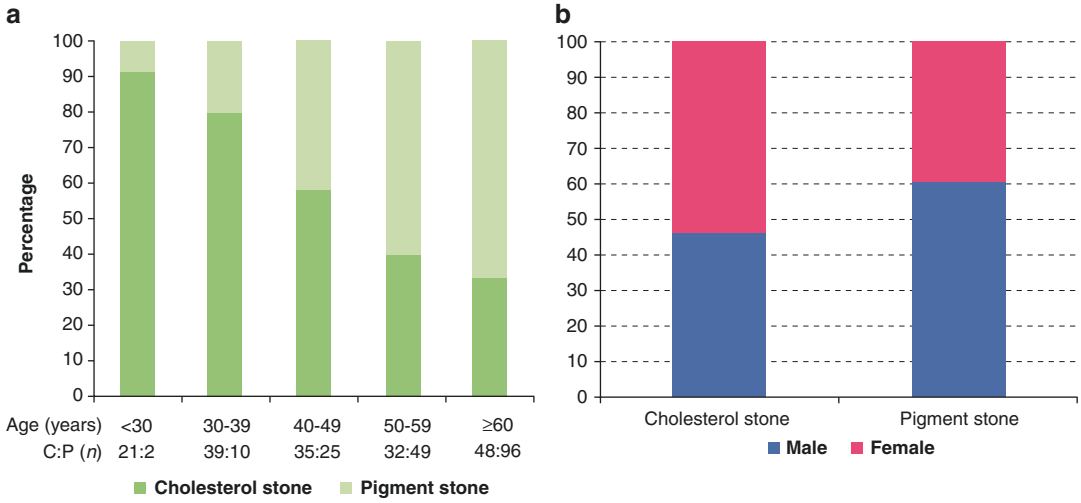

Fig. 12.1 Prevalence of cholesterol and pigment stones with age (**a**) and sex (**b**) in South Korea (adapted from Kim et al. [22])

12.2.1.2 Effects of Estrogen on Cholesterol Gallstones

The prevalence of cholesterol stone is increased by increasing estrogen level dose-responsively [37]. Estrogen can promote cholesterol stones by causing cholesterol supersaturation in bile. Cholesterol stone is prevalent in females during the reproductive age [20]. This effect disappears after menopause [37]. The prevalence of gallstones is increased by the number of pregnancies [49]. Recent meta-analysis including 556,620 populations from 19 studies has reported that the relative risk (RR) for gallstones by estrogen replacement is 1.59 (95% CI, 1.44–1.75) [50]. Among those with estrogen administration, effects of estrogen replacement therapy and oral contraceptives on gallstones are different. Estrogen replacement therapy is a risk factor of gallstones (1.79; 95% CI, 1.61–2.00), while oral contraceptives are not significant (1.19; 95% CI, 0.97–1.45) [50].

12.2.1.3 Coffee Consumption and Gallstones

Gallstone prevalence is reversely correlated with the amount of coffee consumption in several studies [36, 55]. Coffee can promote cholecystokinin secretion in the blood. The main action of cholecystokinin is to increase gallbladder contraction, which inhibits cholesterol crystal formation in the gallbladder. One study has analyzed the correlation between the amount of coffee consumption and the frequency of cholecystectomy and found an inverse correlation in women, but no such correlation in men [36] (Fig. 12.2). Among women, the hazard ratio (HR) was lower in premenopausal women (0.17; 95% CI, 0.05–0.55) and in those with estrogen replacement (0.44; 95% CI, 0.28–0.70) than in others [36]. When the analysis was stratified by gender, the female cohorts yielded significant results comparing coffee consumption with non-consumption (RR 0.83; 95% CI, 0.79–0.88) with no heterogeneity (I^2 = 0.0%; p = 0.685). In contrast, results from the male cohorts did not reach significance (RR 0.83; 95% CI, 0.66–1.03) and had high heterogeneity (I^2 = 70.6%; p = 0.033) [55]. These results suggest that the prevention of gallstones by coffee consumption might be associated with estrogen effect.

12.2.1.4 Physical Activity and Gallstones

Physical activity (PA) levels can independently reduce the prevalence of gallstone disease (GD) [56]. A meta-analysis has reported an inverse association between physical activity and gallstone disease in both men and women (RR 0.85; 95% CI, 0.78–0.92; comparison of the highest-level and the lowest-level groups) [56]. However,

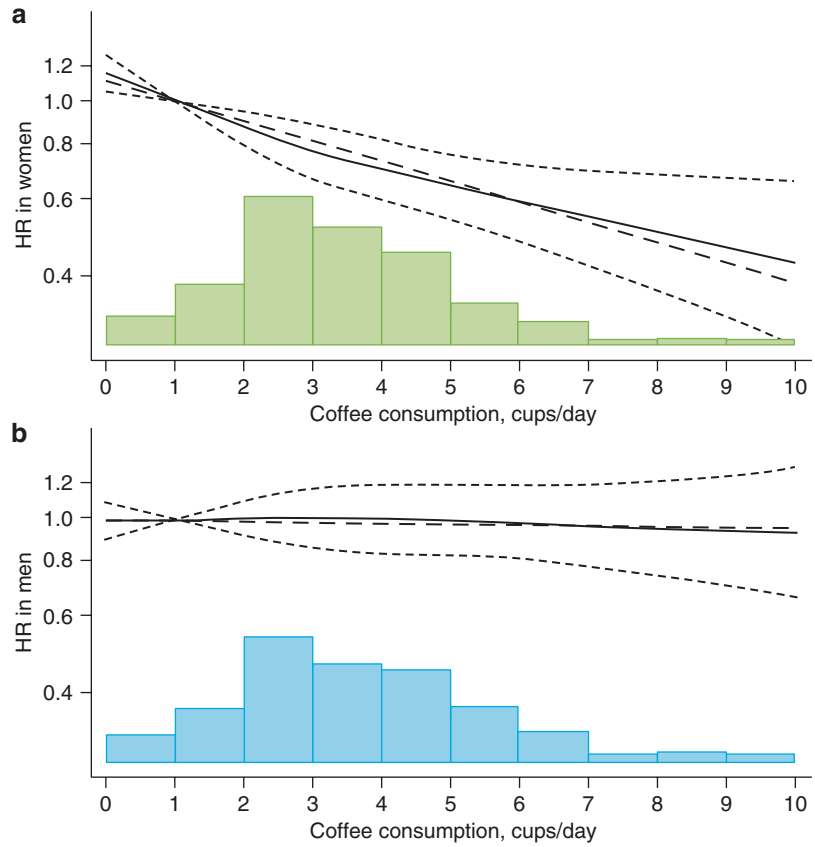

Fig. 12.2 Risk of cholecystectomy by coffee consumption. Solid lines represent HRs, and short dashed lines represent 95% CIs estimated from multivariable restricted cubic spline model in women (**a**) and in men (**b**) (adapted from Nordenvall et al. [36])

one study in Korea [28] has reported that estimated rates of PA and GD are 23.7% and 4.6% in males and 18.4% and 4.2% in females, respectively. Gallstone prevention by PA is associated with males, but not females [28]. It has been suggested that risk factors for GD, such as nonalcoholic fatty liver disease and total cholesterol levels, could be reduced by PA in males. However, for females, estrogen is such a strong risk for GD that effects of PA could be relatively low.

12.2.1.5 Cholecystectomy for Gallstone Disease

GD is one common cause of surgery. In the laparoscopic era, rates of cholecystectomy have increased because of its wide indications [33]. Rates of cholecystectomy between genders are similar. However, clinical characteristics of GD are different between men and women. One study [38] using GallRiks (Swedish Register for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography) has reported that women receive cholecystectomy at a younger age than men (mean age, men vs. women: 51.14 years vs. 46.63 years). Especially, younger women less than 40 years old receive surgery for biliary pain sixfold higher than men. Compared to women, men usually receive surgery for complications of gallstones such as jaundice, acute cholecystitis, acute cholangitis, or biliary pancreatitis [38]. It has been suggested that some women receive surgery not for biliary pain, but for functional gastrointestinal disorders (FGID) [38]. Sometimes, it is difficult to perform differential diagnosis for biliary pain and FGID. Women complain more abdominal pain and need more analgesics for pain relief than men [48]. In addition, conversion rates from laparoscopy to open cholecystectomy and fibrosis by accumulation of collagen tissue near gallbladder are more frequent in men than in women [54]. One study in Australia has reported that men have a later diagnosis of acute cholecystitis than women

(mean age, men vs. women: 66 years vs. 57 years) with more comorbidities [54]. Rates of severe or necrotizing cholecystitis are higher in men than women. However, there are no significant differences in complication rate, mortality, or re-admission rate between genders [35].

12.2.1.6 Positive Association of Gallbladder Stones or Polyps with Colon Polyps

Patients with gallbladder stones or polyps show higher risks of colorectal adenoma in men (odds ratio [OR] 1.47; 95% CI, 1.08–1.98 or 1.56; 95% CI, 1.20–2.02, respectively), but not in women in a study in Taiwan [32]. Gallbladder polyps and colorectal adenomas share some risk factors, such as obesity, glucose intolerance, insulin resistance, metabolic syndrome, and male gender. The gender difference in the relationship between gallbladder polyps and colorectal adenomas might be related to the fact that men have higher insulin resistance, serum levels of insulin-like growth factor 1, and secondary bile acid levels of colon than women. The possible mechanism for the association between gallbladder stones and colonic adenomas remains unclear. Patients with gallbladder stones have more deoxycholic bile acids known to be produced by bacterial degradation in the colon [46]. These secondary bile acids can increase the risk of colorectal neoplasm. Furthermore, secondary bile acid levels are higher in men with colorectal adenomas [4], while exogenous estrogen can decrease secondary bile acid production [10].

12.2.2 Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction (SOD) frequently develops in middle-aged women than in men, which may be caused by increased sensitivity of SOD to cholecystokinin [44]. In an animal experiment, amplitudes of phasic reaction by administration of CCK are increased in males than in females [47]. The rate of post-ERCP pancreatitis (PEP) is higher in women than in men. The hypersensitivity of SOD in women might be one of the mechanisms of PEP [44].

12.3 Benign Diseases in the Pancreas

12.3.1 Pancreatic Cystic Lesions

Detection rates of pancreatic cystic lesions have increased up to 15% in adults due to increased image studies [11]. Serous cystic neoplasm (>75% in females), mucinous cystic neoplasm (>95% in females), and solid pseudopapillary neoplasm (SPN, >80% in females) are developed more frequently in females [11], while intraductal papillary mucinous neoplasm (IPMN) is more frequent in males [19]. Male dominance of IPMN is distinct in Asian countries than in Western countries and in main duct type than in branch duct type [19]. The male-to-female ratio is 3:1 for the main duct type and 1.8:1 for the branch duct type [19].

SPN has sex differences in terms of size and pathology. The mean size of SPN is 5.3 cm in old patients (≥50 years old) and 7.6 cm in younger patients (<50 years old) [27]. This finding suggests that estrogen can promote the growth of SPN [27]. SPN in males is characterized by late diagnosis, smaller size, and more solid proportion than in females [17]. Morphological features of SPN by image analysis show solid type predominant in males (solid type, 81%; mixed type, 19%) and mixed type predominant in females (mixed type: 70%) [17]. Therefore, it is difficult to differentiate SPN from other solid malignancies in the pancreas in males [17]. In another study [15], fibrous capsule and cholesterol cleft are distinct pathologic features of SPN in females. In spite of these pathological differences, prognosis is equivalent between sexes.

12.3.2 Acute and Chronic Pancreatitis

Main causes of acute pancreatitis (AP) include gallstones (35.0%), alcohol drinking (20.4%), and others (44.6%) [8]. However, they are quite different between genders. Alcohol drinking is the main cause of AP in men (alcohol vs. gallstone: 48% vs. 22%), while gallstone is the

dominant cause in women (alcohol vs. gallstone: 9% vs. 66%) [30]. In a Taiwan study enrolling 13,110 patients with acute biliary pancreatitis (ABP), males revealed poor prognosis than females in terms of hospital mortality (RR 1.81; 95% CI, 1.15–2.86), local complications (RR 1.38; 95% CI, 1.05–1.82), gastrointestinal bleeding (RR 1.44; 95% CI, 1.18–1.76), and total parenteral nutrition rate (RR 1.24; 95% CI, 1.00–1.52) [43]. Another nationalwide study for outcomes of patients with acute pancreatitis has also reported that men have higher mortality and morbidity than women [42] (Fig. 12.3). Post-ERCP pancreatitis (PEP) is higher in women than in men (OR 1.40; 95% CI, 1.24–1.58). However, such difference was less significant than other PEP risk factors, including SOD (OR 4.37), previous history of PEP (OR 3.23), previous history of pancreatitis (OR 2.00), precut EST (OR 2.11), and no preventive pancreatic duct stent (OR 2.10) [5].

The prevalence of chronic pancreatitis (CP) was 4.6-fold higher in men than in women in Japan [16]. The main cause of CP was alcohol drinking (61.9%) [8]. The big difference in CP between genders was caused by higher rate of alcohol drinking in men than in women. In Biostatistics of South Korea in 2019, the rate of high-risk drinking was 18.7% in men and 5.6% in women (high-risk drinking was defined as more than two times a week and more than 7 units in males or 5 units in females) [26]. However, women developed serious alcohol-related diseases with a shorter duration or a smaller amount of alcohol drinking than males. The mean duration of alcohol drinking to alcoholic CP was 23.0 years in women and 34.3 years in men [34]. A peak incidence of alcoholic CP was younger in women (aged 35–44 years) than in men (aged 45–54 years) [53]. Mean daily alcohol consumption to induce alcoholic CP was 85.9 g in women and 96.8 g in men [34]. These gender differences are caused by different alcohol metabolism. Men have 1.5-fold higher levels of alcohol dehydrogenase enzymes. They also have higher alcohol detoxication by masculine body composition and higher amount of total body water, which can reduce the level of alcohol concentration after

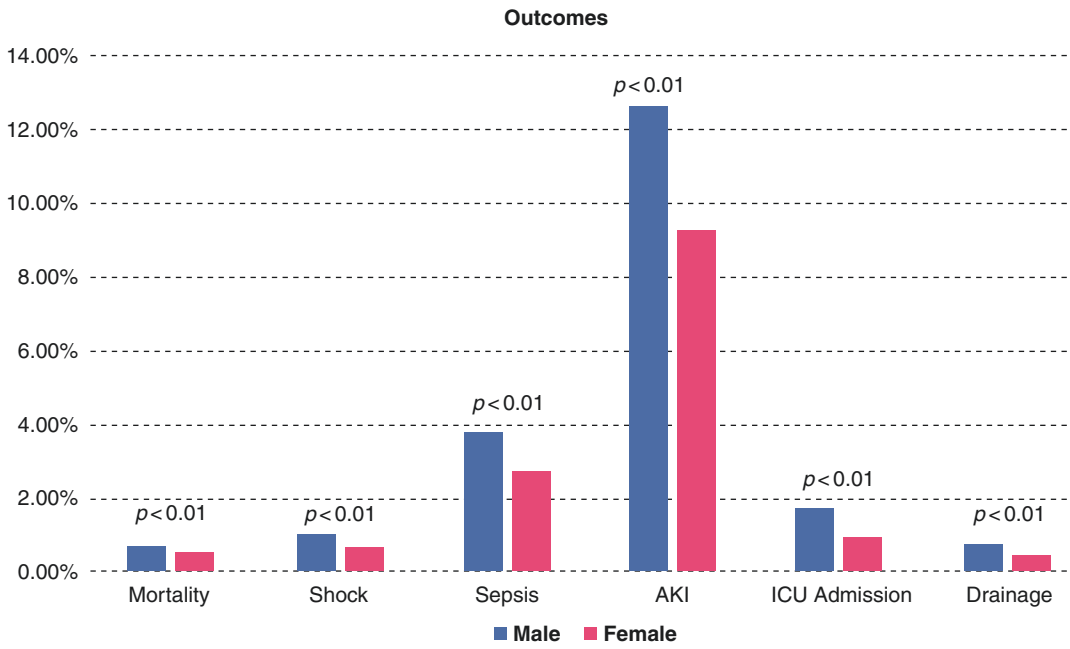

Fig. 12.3 Outcomes in patients with acute pancreatitis: Male vs. female. *AKI* acute kidney insufficiency (adapted from Sharma et al. [42])

drinking. However, women have no such benefits for alcohol metabolism. In addition, estrogen can inhibit alcohol degradation [9].

One study [41] about effects of smoking on pancreatitis has reported that more than 20 pack-year is a risk factor in both genders, while the risk is greater in women than in men. HRs of smoking for non-biliary AP and recurrent AP or CP were 2.01 (1.45–2.80) and 3.22 (2.12–4.87) in women and 1.87 (1.34–2.60) and 1.72 (1.12–2.66) in men, respectively [41].

12.4 Malignancies in the Pancreas and the Biliary Tract

12.4.1 Pancreatic Cancer

Cancer statistics 2018 in South Korea reported that pancreatic cancer was diagnosed in 4020 men and 3591 women. Age-standardized incidence rate (ASR, number of patients per 10^5 population) was 9.0 for men and 6.5 for women [25]. Sex hormone might play a role in the man dominance of pancreatic cancer. Epidemiologic data have revealed that sex difference in pancreatic cancer is greater in the young population and smaller in the old population [25]. Women who have received oophorectomy show higher incidence of pancreatic cancer than other women who have not received oophorectomy [2]. These data suggest that estrogen can inhibit the development of pancreatic cancer, while androgen promotes it. In animal experiments, estrogen replacement is effective in inhibiting the development of pancreatic cancer [1]. Female rats showed less production of oxidative stress than male rats after they are fed a high-lipid diet [1]. However, unmatched results have reported that estrogen receptor does not exist in normal pancreas and that tamoxifen, an estrogen receptor antagonist, has no effect on pancreatic cancer development [2]. In spite of controversial results, it has been suggested that estrogen can inhibit pancreatic cancer development, although the mechanism and clinical significance have not been established yet.

12.4.2 Gallbladder and Biliary Tract Cancer

Cancer statistics 2018 in South Korea reported that gallbladder and biliary tract cancer were diagnosed in 3840 men and 3339 women. ASR was 8.3 for men and 5.3 for women [25]. However, when gallbladder cancer and biliary tract cancer were analyzed separately, gallbladder cancer (GBC) showed no difference between sexes [51], while biliary tract cancer was male dominant.

The GBC is a fatal malignancy. It displays considerable differences in certain ethnicities and geographic regions. GBC is about two times more common in women than in men [40]. Female predominance of GBC is caused by high prevalence of gallstones, estrogen effect, and genetic background. However, in South Korea, the incidence of GBC showed no significant difference between sexes (female-to-male incidence rate ratio: 0.96) [51]. Anomalous union of pancreaticobiliary duct (AUPBD), one of the risk factors of GBC, was frequently developed in Asian countries and in females. In addition, GBC developed more frequently in females with AUPBD than in males with AUPBD (female vs. male: 83% vs. 44%) [21].

The incidence of bile duct cancer (BDC) was male dominant with some variations between countries. South Korea had the highest incidence of BDC, showing a male dominance for intrahepatic BDC (M:F = 1.9:1) and extrahepatic BDC (M:F = 2.5:1) [12].

12.5 Morbidity and Mortality of Major Surgeries for Pancreas and Biliary Diseases

In a retrospective study, mortality rate after major surgery for gastrointestinal diseases was lower in women than in men [39]. In emergent abdominal surgery, women showed less mortality than men for diseases with a mild to moderate severity (men 25% vs. women 10%), while there was no

difference in mortality for severe diseases [14]. It has been suggested that estrogen can promote the secretion of pro- or anti-inflammatory cytokines from macrophages, while male sex hormone inhibits such secretion [3, 52].

12.6 Normal Structures of Pancreas and Biliary Tracts

12.6.1 Pancreas

Pancreas volume in normal adults is 71–83 cm^3, showing no statistically significant difference between males and females [7, 24]. Another study has revealed that total volume and head portion of the pancreas are smaller in females than in males, while body and tail volumes of the pancreas are not different between sexes [24]. However, the size of the pancreas has more variations among individuals than that between sexes [45], suggesting that the sex difference in pancreas volume is minimal.

12.6.2 Biliary System

The dilation of the common bile duct (CBD) helps distinguish obstructive from non-obstructive causes of jaundice. Availability of normal measurements of the CBD is therefore important. Diameter of CBD measured by abdominal ultrasound is less than 6 mm for 95% of subjects (range, 2.0–7.9 mm, proximal of 4.0 mm and distal of 4.2 mm). It increases with old age, showing no difference between sexes [29].

12.7 Conclusions

In this chapter, sex/gender differences in pancreas and biliary diseases such as gallstones, cholecystitis, pancreatitis, and malignancies are summarized with literature reviews (Table 12.1 and Fig. 12.4). The main causes of these differences are effects of estrogen and environmental factors such as alcohol drinking, smoking, and obesity. Epidemiologic data have revealed some

Table 12.1 Summaries of sex/gender difference in pancreas and biliary diseases

Pancreas and biliary diseases	Female	Male
Gallstone	Western: two to three times prevalent Asian: equal prevalence	Western: less frequent Asian: equal prevalence
	Increased incidence by estrogen replacement	
	Decreased incidence by coffee consumption	Unchanged incidence by coffee consumption
Cholecystectomy	At younger age and more frequent biliary pain	At older age and more frequent comorbidity and severe course
Sphincter of Oddi dysfunction	Frequent at middle aged Cause of post-ERCP pancreatitis	–
Anomalous union of pancreaticobiliary duct	More frequent and more related with gallbladder cancer	–
Pancreas cystic neoplasm	More frequent serous and mucinous cystic neoplasm and solid pseudopapillary neoplasm	More frequent intraductal papillary mucinous neoplasm
Acute pancreatitis	Cause: alcohol 9%, gallstone 66%	Cause: alcohol 22%, gallstone 48% More severe and poorer prognosis
Chronic pancreatitis	Less frequent alcoholic cause Shorter duration and smaller cumulative amounts of alcohol	More frequent alcoholic cause
Pancreatobiliary surgery	Better prognosis after surgery	–
Pancreatic cancer	–	Higher incidence
Bile duct cancer	–	Higher incidence

ERCP endoscopic retrograde cholangiopancreatography

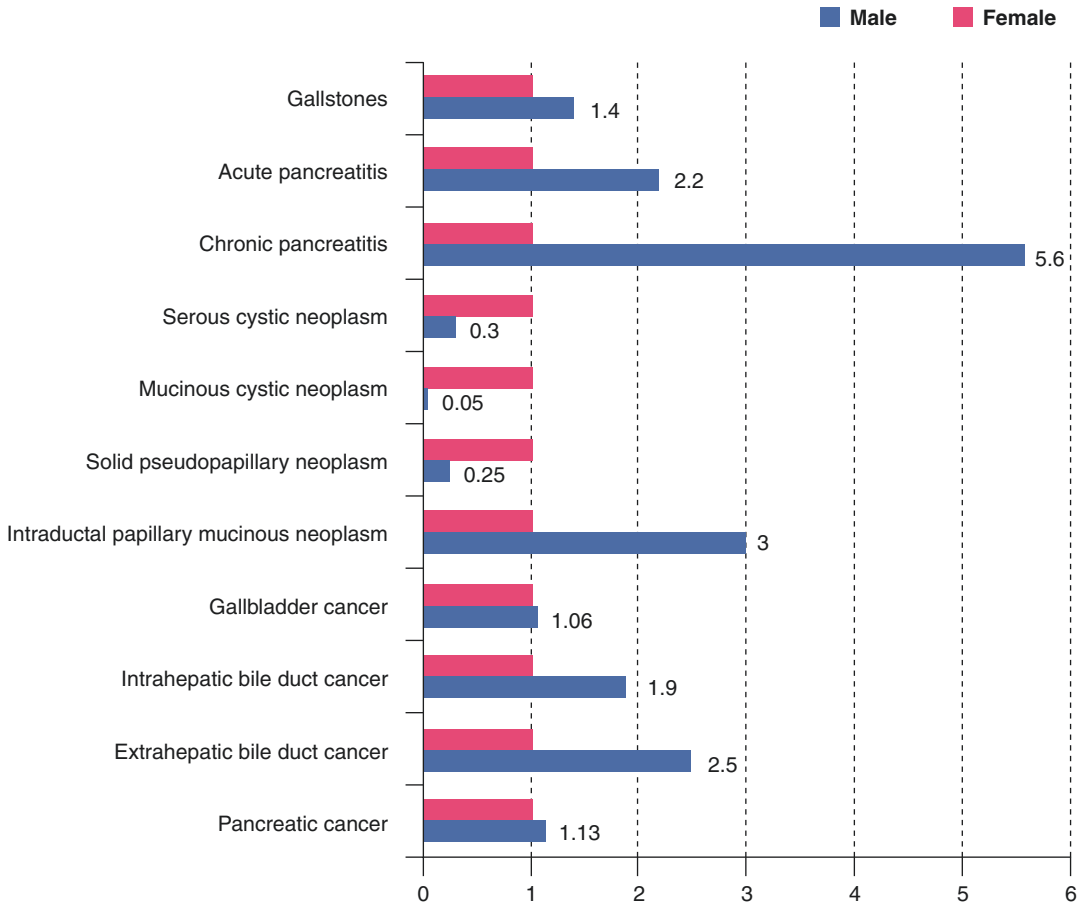

Fig. 12.4 Male-to-female prevalence rate ratio in pancreas and biliary diseases in South Korea

sex/gender differences in pancreas and biliary disease between Eastern and Western countries because of different genetic backgrounds as well as differences in food preferences and obesity rates. Gender medicine in this field is not enough to use for clinical decision-making. It has been studied in limited fields such as epidemiology, risk factors, and pathology. In addition, most studies were small retrospective studies or animal experiments. In the near future, studies about gender medicine are needed for personalized medicine in this field.

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Part VII

Liver

Nonalcoholic Fatty Liver Disease

13

Jihyun An

13.1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is a global public health concern, and the leading cause of chronic liver disease, especially in developed countries [1]. NAFLD is characterized by lipid accumulation in the liver not attributed to other causes [2]. NAFLD encompasses simple steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis. NAFLD is prevalent among subjects with obesity, dyslipidemia, diabetes mellitus, and metabolic syndrome. Although NAFLD occurs in both genders, unique gender-related differences exist, especially in women and their hormonal status. Understanding the effects of gender differences on epidemiology, natural course, risk factors, pathogenesis, and treatment in NAFLD is essential for establishing medical and socioeconomic policies for relevant disease management. Such knowledge may also enable healthcare providers to tailor their strategies for the evaluation and management of women with NAFLD. This article specifically focuses on the influence of gender in NAFLD based on existing clinical and epidemiological data and recently published international guidelines.

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13.2 Definition of Nonalcoholic Fatty Liver Disease

NAFLD is characterized by excessive hepatic fat accumulation without other recognized causes of increased fat content (e.g., alcohol, virus, drugs, and autoimmunity). According to the Clinical Practice Guidelines of the European Association for the Study of the Liver, the diagnosis of NAFLD requires the exclusion of daily alcohol consumption >30 g for men and >20 g for women [3]. Alcohol consumption above these limits indicates alcoholic liver disease.

NAFLD includes a broad spectrum of conditions, including nonalcoholic fatty liver (NAFL), NASH, and NASH cirrhosis [4] (Fig. 13.1). NAFL was defined as the presence of steatosis in >5% of hepatocytes based on histological examination without evidence of hepatocellular injury in the form of hepatocyte ballooning [5]. NASH is distinguished from NAFL by the presence of hepatocellular injury characterized by lobular inflammation and hepatocellular ballooning. This inflammation is associated with the initiation and progression of fibrosis. NASH cirrhosis is characterized by cirrhosis associated with NAFL or NASH or cirrhosis occurring in patients with NAFL or NASH as proven by past histology.

Based on a recent expert consensus, NAFLD does not reflect current knowledge of pathogenesis and was therefore designated as metabolic (dysfunction)-associated fatty liver disease

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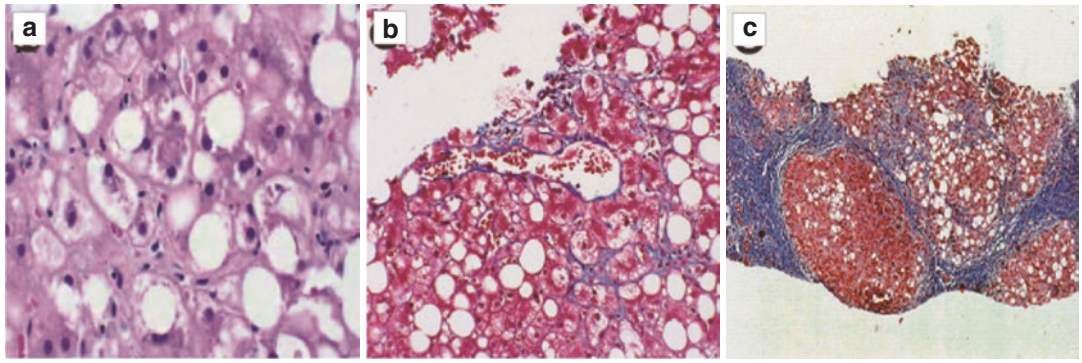

Fig. 13.1 Histological stages of nonalcoholic fatty liver disease. (**a**) simple steatosis, (**b**) steatohepatitis, (**c**) liver cirrhosis (adapted from Suzuki and Abdelmalek [4])

(MAFLD) [6]. The diagnosis of MAFLD is based on evidence of fat accumulation in the liver in the presence of one of the following three criteria: overweight/obesity, type 2 diabetes mellitus (T2DM), and metabolic dysfunction.

13.3 Epidemiology of Nonalcoholic Fatty Liver Disease

NAFLD incidence has rarely been measured. It was 20–86/1000 person-years based on ultrasound (US) with or without elevated liver enzymes [7]. According to a meta-analysis of studies conducted in Asia, the pooled annual NAFLD incidence rate was 50.9 (95% CI, 44.8–57.4) cases per 1000 person-years [8].

In parallel with the obesity and metabolic syndrome epidemic, there has been a rise in NAFL and more advanced diseases. Currently, it is estimated that the prevalence of NAFLD worldwide is approximately 25% [1]. A recent meta-analysis of studies involving 8,515,431 individuals globally reported that NAFLD was highly prevalent in all continents, and the highest prevalence was reported from South America (31%) and the Middle East (32%), whereas the lowest prevalence was reported from Africa (14%) [9] (Fig. 13.2). More than 80 million individuals are affected in the United States. Similar rates are observed in Asia, with a pooled prevalence rate of 27.4% [8].

The prevalence of NAFLD varies with age, sex, ethnicity, and diagnostic method [7]. In general adult populations, the overall NAFLD prevalence is higher in men than in women. In a study of urban population including 2287 subjects from a multiethnic sample (32.1% white, 48.3% black, and 17.5% Hispanic), hepatic steatosis was more significant in men than in women among whites, but not in blacks or Hispanics [10]. When considering the reproductive status, the prevalence and incidence are higher in men than in premenopausal women, while they tend to become more common in women after menopause [11]. In a recent meta-analysis of 17 population-based studies, the prevalence of NAFLD was 19% higher among men than in women [12] (Fig. 13.3). However, among individuals with established NAFLD, women were as likely as men to manifest NASH and more likely to exhibit advanced fibrosis than men. Among patients with NAFLD, women had a 37% higher prevalence of advanced fibrosis than men. Subgroup analysis by age showed differences in relative risk (RR), with an estimated prevalence of 17% higher among women compared with men in studies that included older patients (average study population age >50 years; RR 1.17; 95% CI, 1.01–1.36) but was not significantly higher among women in studies involving younger patients (average age <50 years; RR 0.90; 95% CI, 0.76–1.07). Postmenopausal women on hormone replacement therapy (HRT) had a lower prevalence of NAFLD compared with postmenopausal women not exposed to HRT. In a randomized clinical trial, combined HRT significantly decreased aminotransferase levels in postmenopausal women

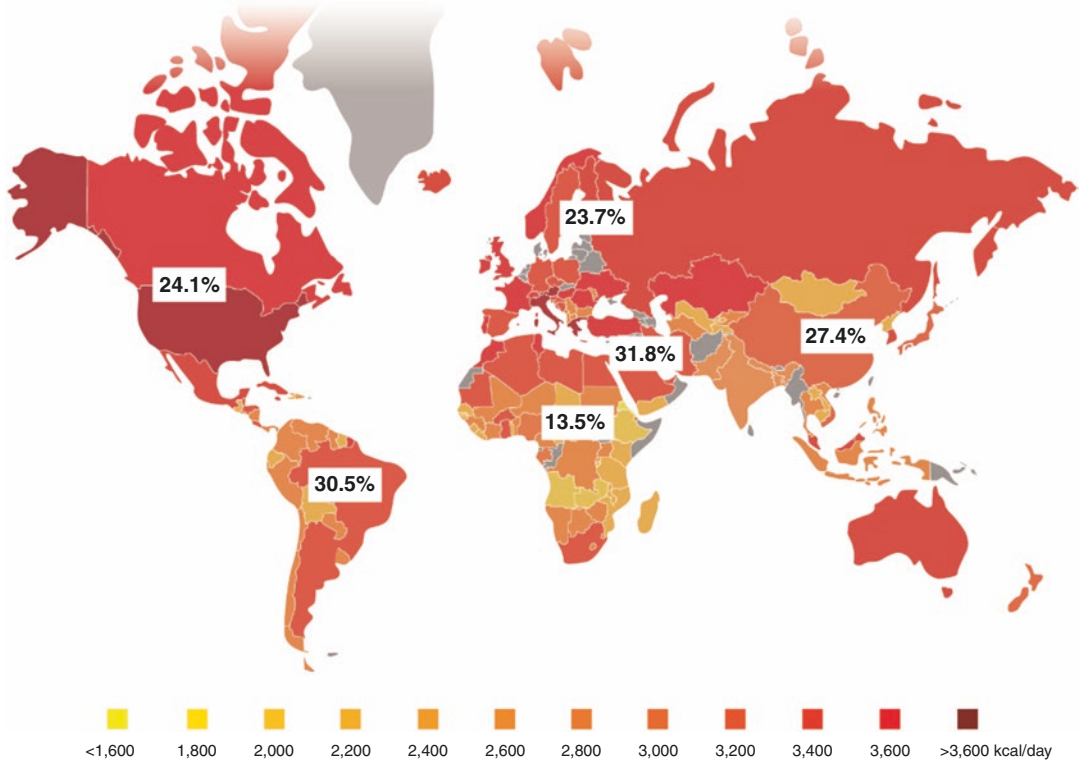

Fig. 13.2 Distribution of global prevalence of nonalcoholic fatty liver disease (adapted from Rinella and Charlton [9])

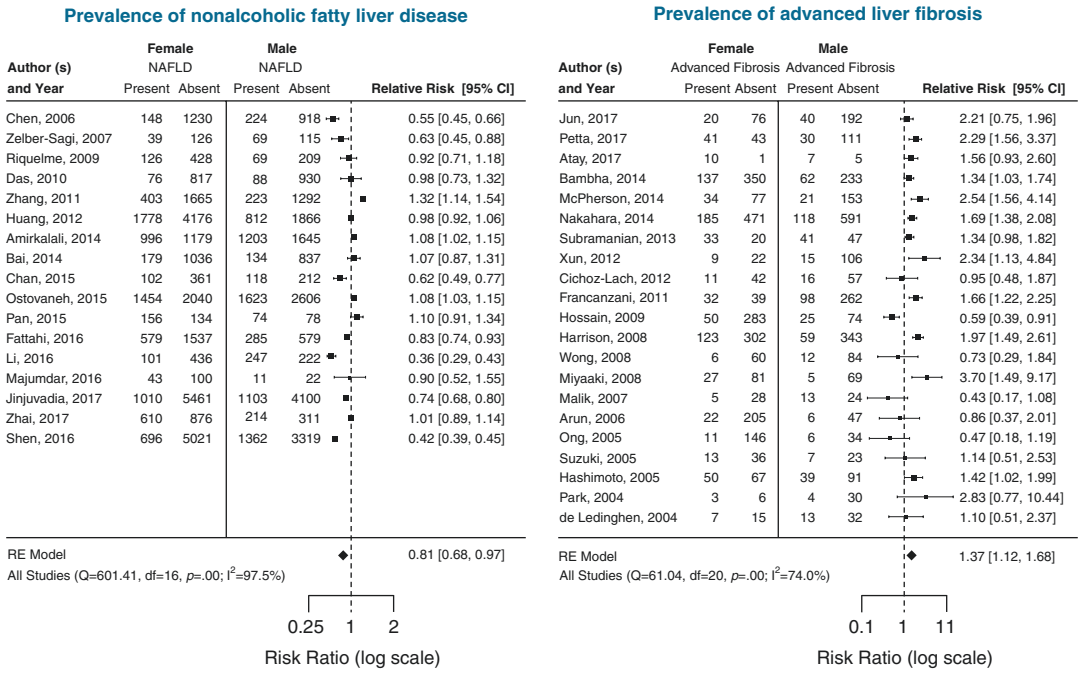

Fig. 13.3 Prevalence of nonalcoholic fatty liver disease and advanced liver fibrosis according to gender differences (adapted from Balakrishnan et al. [12])

with T2D and presumed NAFLD compared with placebo controls [13]. Collectively, the current evidence suggests that women carry a lower risk of NAFLD than men, although the risk appears to rise after menopause. Once NAFLD is established, a woman's risk of progressive disease (NASH and advanced fibrosis) is higher than that of men, especially after age 50 years.

13.4 Natural Course and Cause of Death in Nonalcoholic Fatty Liver Disease

NAFLD is strongly associated with insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease, indicating that NAFLD is a multisystem disease. According to the US National Vital Statistics System, the mortality rate associated with NAFLD increased in the past decade [14]. In a meta-analysis, a higher mortality rate was observed in patients with NAFLD than in the general population [15]. The major causes of death were cardiovascular disease (CVD), malignancy, and liver disease, and liver disease-related deaths increased in the presence of steatohepatitis. In a cohort study of NASH patients, an average of 21–26% of patients progressed to cirrhosis in 8 years [16]. The number of patients with end-stage liver disease caused by NAFLD on the liver transplantation waitlist tripled from the last decade, making NAFLD the second most common indication for liver transplantation [17]. Also, NAFLD is an attributable cause of hepatocellular carcinoma (HCC), and the number of cases of NAFLD-related HCC has rapidly increased in the United States by 9% per year [18]. According to a multi-national study of 458 patients with biopsy-confirmed NAFLD along with bridging fibrosis or compensated cirrhosis, male sex was positively associated with worse survival (adjusted hazard ratio [aHR] 1.87) and greater incidence of HCC (aHR 7.28). Further, the development of HCC without fibrosis was more frequently observed in men than in women.

Several studies have demonstrated that CVD is the leading cause of death in NAFLD, surpassing liver-related death [19]. General population studies have shown differences in the pathophysiology of CVD between men and women, supporting the concept of female hormonal protection in CVD [20]. In the cross-sectional study of clinical and subclinical CVD outcomes in the Framingham Heart Study cohorts, the association between hepatic steatosis and abdominal artery calcium, the independent risk for future CVD was stronger in men than in women [21]. However, a recent US cohort study demonstrated that women with NAFLD lose their cardiovascular protection conferred by the female sex [22] (Fig. 13.4). Among those with NAFLD, cardiovascular disease and mortality were strikingly higher in women than in men. Further studies with more significant numbers of prospective clinical CVD outcomes are necessary to determine whether gender-specific hepatic steatosis is associated with incident CV outcomes and the development of clinical and subclinical CV outcomes.

Malignancy is the second most frequent cause of death after cardiovascular disease among patients with NAFLD. The large cohort study from Korea demonstrated that subjects with NAFLD had higher incidence rates of all cancers than those without NAFLD [23]. Especially, NAFLD was associated with the development of colorectal cancer (HR 2.01; 95% CI, 1.10–3.68) in males and breast cancer (HR 1.92; 95% CI, 1.15–3.20) in females [23] (Fig. 13.5).

13.5 Metabolic Disorders Related to Nonalcoholic Fatty Liver Disease

NAFLD is closely related to obesity, diabetes, dyslipidemia, and metabolic syndrome. Obesity is a well-known risk factor for NAFLD. Bone body index and waist circumference, a measure of visceral adiposity, are positively correlated with the presence of NAFLD [24]. Metabolic syndrome, which consists of abdominal obesity, impaired fasting blood sugar, hypertriglyceridemia, low high-density cholesterolemia, and hypertension, is a major risk factor for NAFLD [2]. NAFLD prevalence was also high in patients with diabetes (60–75%) and dyslipidemia (50%). The prevalence of

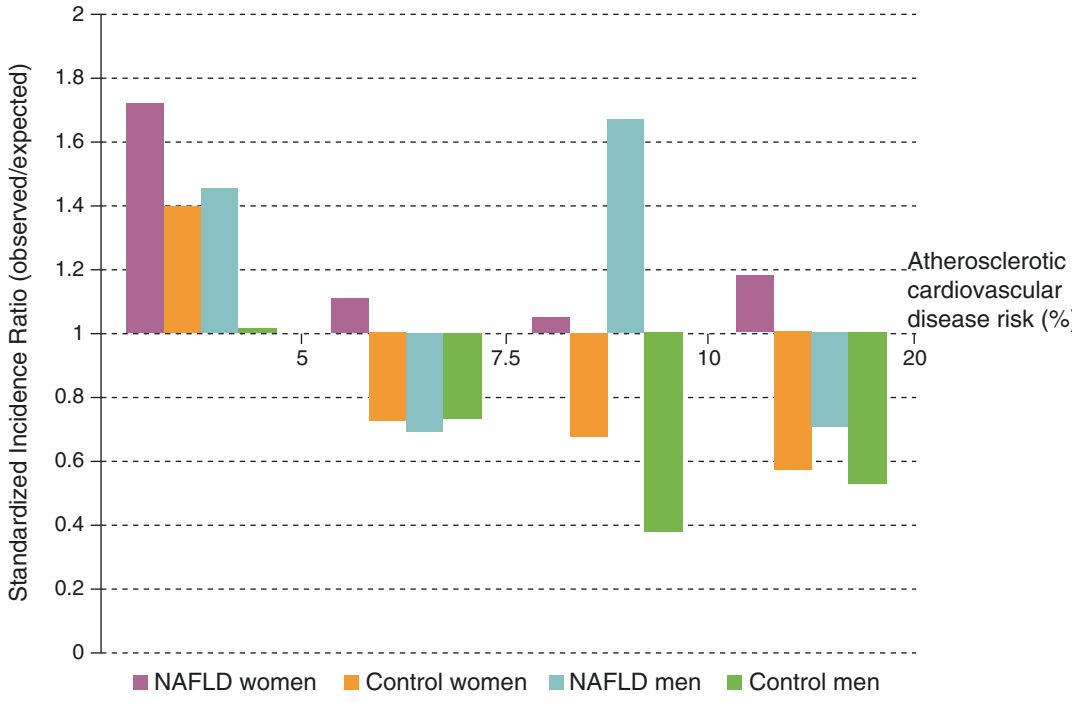

Fig. 13.4 Standardized incidence ratio (observed/expected rate of events) of 10-year risk of myocardial infarction or stroke in men and women with NAFLD compared with the general population (adapted from Allen et al. [22])

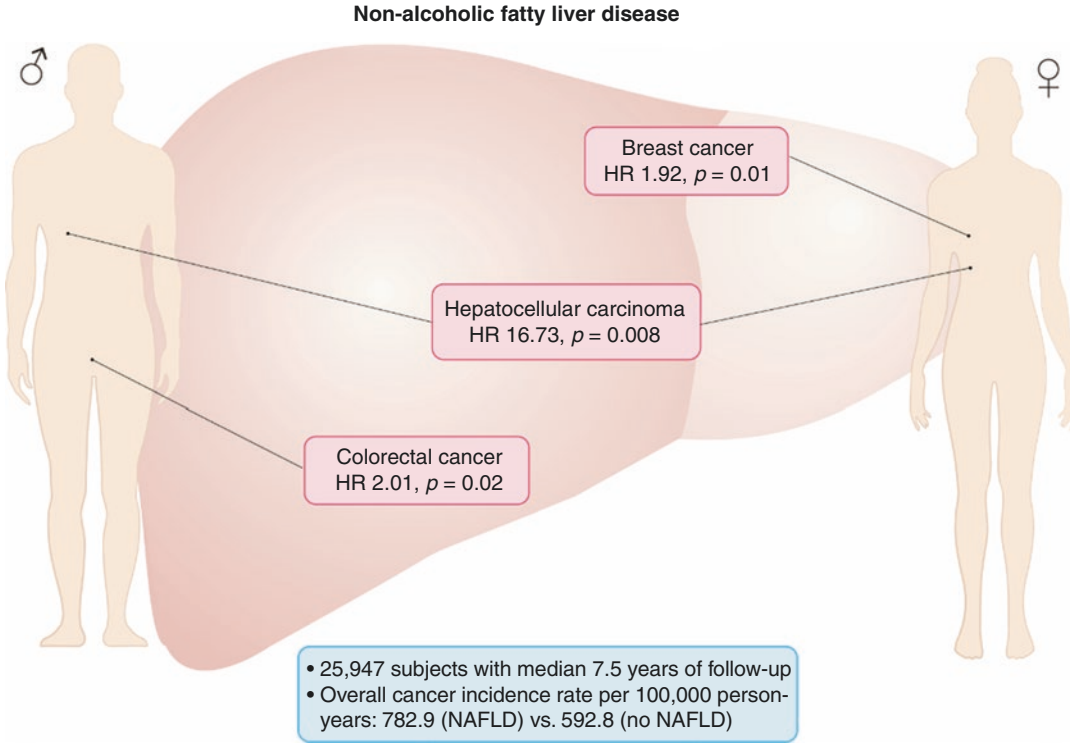

Fig. 13.5 Incidence of malignancy in nonalcoholic fatty liver disease according to gender difference (adapted from Kim et al. [23])

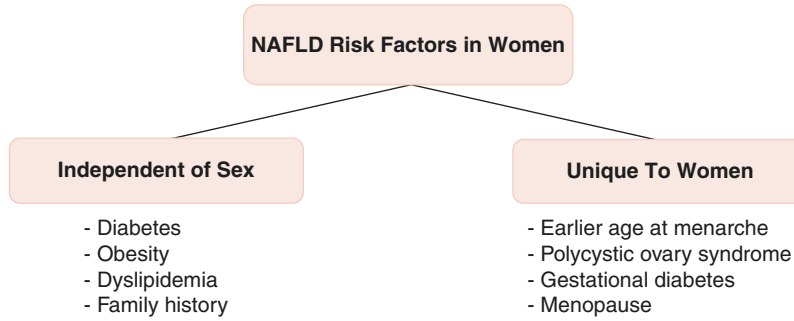

Fig. 13.6 NAFLD risk factors in women (adapted from Yuan et al. [26])

NAFLD increases by 1.6-fold in the presence of hypothyroidism [25]. In addition, obstructive sleep apnea, hypopituitarism, hypogonadism, pancreatoduodenal resection, and psoriasis increase the prevalence and severity of NAFLD [2].

Women exhibit unique risk profiles of NAFLD, including hormonal milieu and reproductive factors [26] (Fig. 13.6). Menopausal status appears to promote NAFLD, independent of chronologic aging. The menopausal transition is associated with decreased energy expenditure and increased visceral adiposity, being a key risk factor for insulin resistance and NAFLD. In a large case-control study from Europe, oophorectomy before age 50 years was associated with a 50% increased risk of NAFLD [27]. Recent data in premenopausal women with histologically confirmed NAFLD also show an increased risk of NASH fibrosis in women with polycystic ovary syndrome, independent of age and obesity [28]. Recent cohort studies reported that gestational diabetes is associated with the risk of NAFLD prevalence in middle-aged women [29]. Otherwise, a longer duration of breastfeeding was protective against NAFLD in women [30].

13.6 Pathogenesis of Nonalcoholic Fatty Liver Disease

13.6.1 Adipose Tissue and Skeletal Muscle

Regional fat distribution is associated with metabolic disorders and NAFLD, with a lower risk resulting from gynoid fat distribution in the gluteofemoral subcutaneous area and a higher risk with android visceral adiposity [31]. In contrast to gluteofemoral subcutaneous fat in women, visceral adiposity occurs in men, indicating the higher prevalence of NAFLD in men than in premenopausal women [11] (Fig. 13.7). Estradiol lowers lipolysis and improves adipose tissue insulin sensitivity, reducing excessive delivery of fatty acids to the liver. Serum adiponectin levels are higher in women than in men regardless of menopausal status [32]. These hormones are protected from the adverse consequences of excessive fat storage in women, especially during premenopausal years [33].

Skeletal muscle is one of the major organs responsible for peripheral glucose disposal and is generally more insulin-sensitive in women than in men [34]. Thus, sarcopenia in women is often associated with insulin resistance, proinflammatory cytokines, and the lack of anabolic hormones [35]. Skeletal muscle expression of estrogen receptor-α is markedly reduced in women with metabolic syndrome, indicating the relationship between sarcopenia and the development of NAFLD in women.

13.6.2 Estrogen

In an NAFLD registry study based on histological examination, premenopausal women exhibited more severe lobular inflammation, hepatocyte ballooning, and Mallory-Denk bodies than postmenopausal women or men [36]. Estrogen increases the number of T cells and regulatory T cells and modulates hepatic injury and

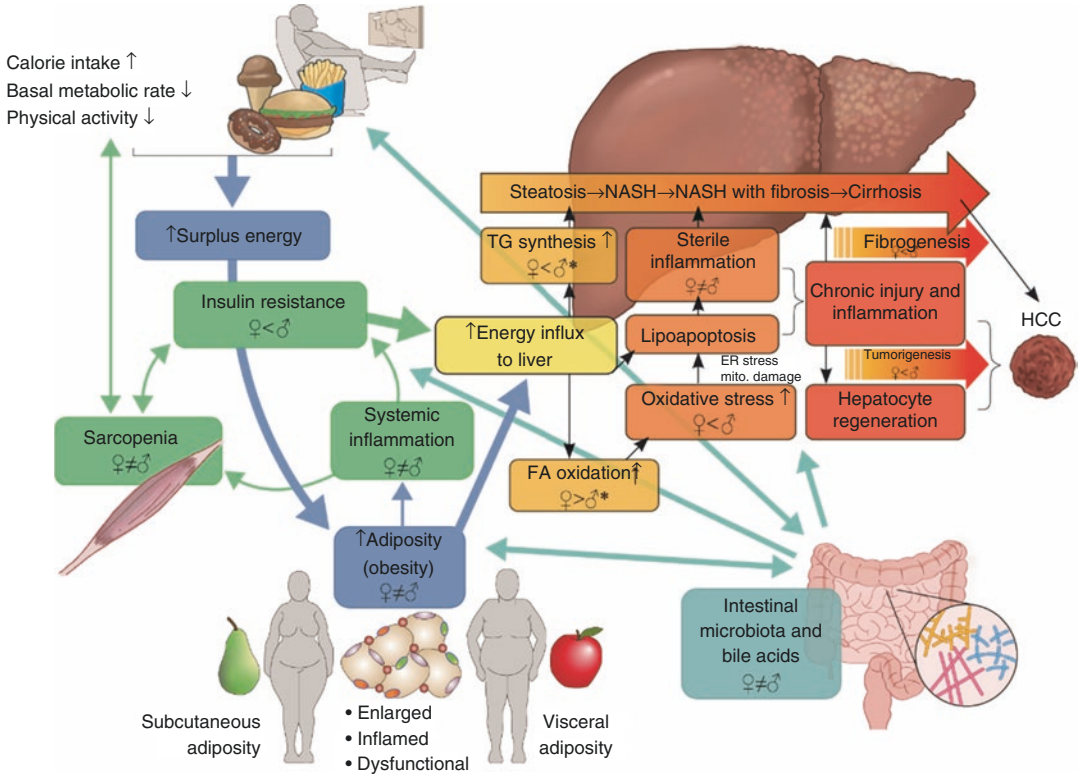

Fig. 13.7 Differences in the pathophysiology of nonalcoholic fatty liver disease according to gender (adapted from Lonardo et al. [11])

inflammation. Although premenopausal women exhibit severe hepatic damage, the hepatic fibrosis is lower than in men and postmenopausal women, suggesting multiphasic effects of sex hormones on NAFLD pathogenesis [36].

Estrogens bind to estrogen receptors within target cells and translocate into the nucleus where they regulate gene expression [37] (Fig. 13.8). In hepatocytes, estrogen alleviates lipotoxic stress by suppressing de novo lipogenesis and promoting oxidation. Estrogen decreases the expression of lipogenesis-related genes, such as *FAS*, *ACC*, *SCD*, and *SREBP*, along with over-expression of oxidation-related genes. In Kupffer cells, estrogen inhibits the production of IL-6 and the secretion of proinflammatory cytokines, eventually reducing inflammation. In hepatic stellate cells, estrogens upregulate apoptosis-related genes and downregulate profibrotic genes, such as SMA, collagen, and matrix metallopeptidases, thereby attenuating liver fibrosis.

13.7 Treatment of Nonalcoholic Fatty Liver Disease

Lifestyle interventions, including dietary modification and exercise, remain the cornerstone of NAFLD treatment. Pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis. The role of sex differences in treatment response in NAFLD remains to be investigated. Based on the differences in pathogenesis of NAFLD/NASH between men and women, a gender-specific approach to the development and application of drugs should be considered. Additionally, sex- and age-based therapeutic strategy is needed due to the increased

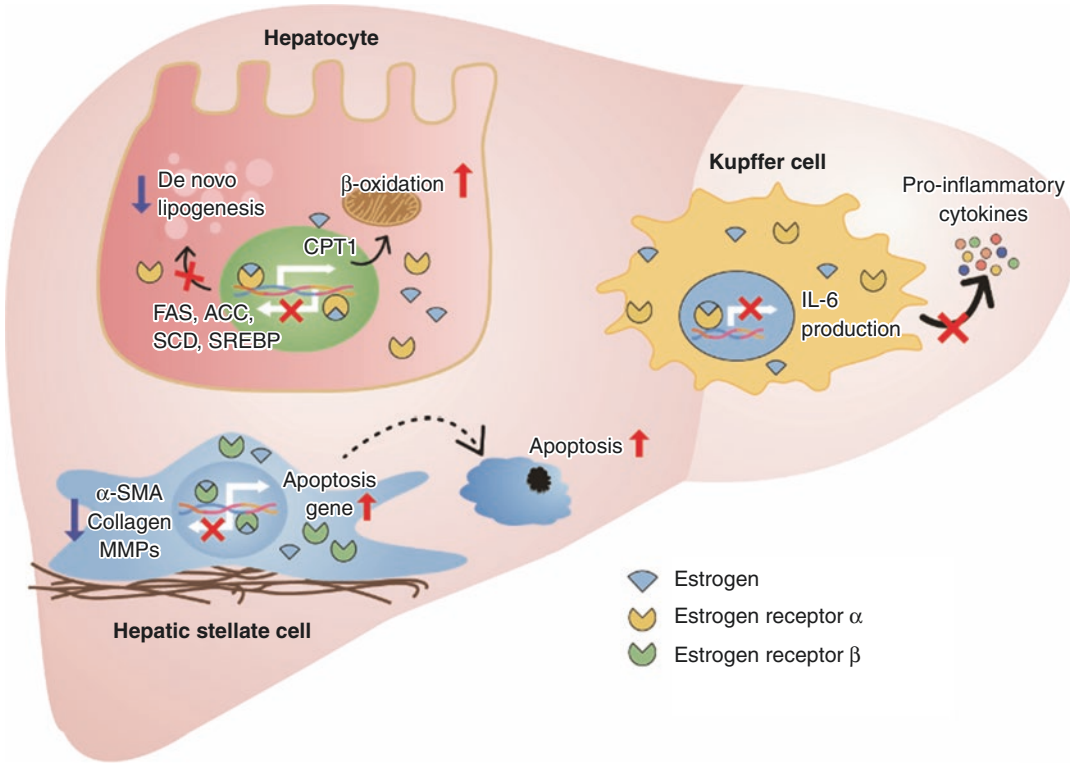

Fig. 13.8 A schematic diagram presenting the protective mechanisms of estrogen in the liver (adapted from Lee et al. [37])

incidence and severity of NAFLD among postmenopausal women.

13.7.1 Weight Reduction

Weight loss significantly reduces liver fat content in obese patients with NAFLD. Weight loss greater than 7% decreased the intrahepatic fat content and inflammation and resulted in remarkable histological improvement. In obese patients with NAFLD, the rate of weight loss affects steatohepatitis [38]. However, in a recent study evaluating changes in NASH in response to weight loss following a 12-month lifestyle intervention, female sex was associated with a lower chance of NASH improvement in individuals losing 7–10% of body weight [39]. However, patients with greater than 10% of body weight loss, independent of sex, showed improved NASH, suggesting a potential need for more significant weight loss targets in women.

The approach to weight reduction among older women requires special attention. Significant weight reduction accelerates the loss of lean tissues, skeletal muscle, and bone mass among older subjects, which may trigger osteoporosis and bone fracture [40]. Also, the required weight loss necessary to achieve regression of NAFLD among postmenopausal women has yet to be defined. Integrating dietary modification with routine exercise is important in order to avoid adverse loss of lean mass. Both aerobic and resistance training prevent bone loss during weight loss [4].

13.7.2 Dietary Therapy

Dietary recommendations should consider caloric restriction and exclusion of NAFLD-promoting ingredients including processed food and beverages high in fructose. A daily intake of 1500–1800 kcal in men and 1200–1500 kcal in

women can reduce total energy intake by more than 500 kcal/day [41]. However, daily caloric intake should be optimally adjusted according to age, sex, weight, and physical activity.

Macronutrient (carbohydrates, fats, and proteins) composition is associated with the development of obesity and NAFLD. Carbohydrate intake was related to the severity of intrahepatic inflammation, while low-carbohydrate diets effectively reduce liver fat content [42]. The macronutrient composition should be adjusted according to the Mediterranean diet with high content of monounsaturated fatty acids. Although women consume more fruits and vegetables than men, they also have a higher intake of sugars, underscoring the need for gender-specific dietary modification.

13.7.3 Drug Treatment

13.7.3.1 Vitamin E (Alpha-Tocopherol)

Vitamin E decreases oxidative stress (which worsens NASH) and thereby improves liver inflammation. In the PIVENS phase 3 trial, the administration of 96-week high-dose vitamin E (800 IU/day) produced significant improvement in liver histology compared with placebo [43]. However, the long-term use of vitamin E is associated with safety concerns because of the increased risk of prostate cancer [44]. Although the additional risk of prostate cancer by vitamin E was not clearly demonstrated in further studies, vitamin E can be used safely in women with NAFLD.

13.7.3.2 Insulin Sensitizers

Thiazolidinediones (rosiglitazone, pioglitazone), PPAR-γ agonists, reduce insulin resistance in the liver, muscle, and adipose tissue and decrease hepatic fat and hepatocellular injury by alleviating hepatic mitochondrial oxidative dysfunction. In several randomized controlled studies reported recently, histologic improvement in hepatocellular damage was observed in thiazolidinedione-treated patients. Unfortunately, no improvement in liver fibrosis was observed [43, 45]. Bone loss in women treated with thiazolidinediones is a possible concern [46].

Metformin is considered as first-line treatment for diabetes mellitus in patients with NAFLD [47]. Metformin reduces insulin resistance in the liver and muscles. Also, metformin inhibits hepatic fat accumulation and glucose excretion. Sex differences in the treatment outcomes of NAFLD based on insulin sensitizer have yet to be reported.

13.7.3.3 Lipid-Lowering Agents

Cardiovascular disease is the most common cause of death in patients diagnosed with NAFLD, suggesting the need for modification of cardiovascular risk factors. Lipid-lowering agents such as statins can be considered in NAFLD patients with dyslipidemia. In a study using the National Health Information Database of Korea, statin treatment decreased the risk of NAFLD as well as the development of related fibrosis [48].

13.7.3.4 Hormone Replacement Therapy (HRT)

Drugs targeting sex hormones represent potentially unique treatment targets in women diagnosed with NAFLD. A randomized controlled trial of HRT in women with diabetes and concomitant NAFLD improved the elevated liver enzymes among HRT users, supporting the potential protective role of exogenous estrogen supplementation in hepatic inflammation [13]. However, the safety and long-term effect of HRT in postmenopausal women remain largely unexplored.

13.8 Conclusions

The epidemic of NAFLD continues to increase in parallel with the ongoing rise in obesity. The impact of NAFLD will be reflected in higher rates of end-stage liver disease, HCC, the need for liver transplantation, and liver-related death. Although the prevalence of NAFLD in women is lower than in men, it tends to increase after menopause. However, once NAFLD is established, a woman's risk of advanced fibrosis is

higher than in men. Sex hormones, distribution of adipose tissue, and skeletal muscle may play a role in gender-specific development and progression of NAFLD.

In previous NAFLD trials, sex differences in treatment response were rarely explored. Evaluation of differences in sex, gender, and hormonal status will lead to a better understanding of NAFLD risk, therapeutic targets, and treatment response.

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Chronic Liver Disease

14

Won Kim

14.1 Introduction

Sex-specific medicine pursues a goal that both male and female individuals would receive the best tailored treatment based on scientific evidence. Sex differences yield substantial biological variations in chronic liver disease. Biological sex differences, including hormonal status and body fat distribution, as well as sociocultural traits, such as dietary patterns and physical activity, influence the development and progression of chronic liver disease [1]. In this regard, biological sex differences that may affect the clinical course of chronic liver disease merit further investigation.

Sex-specific medicine focuses on the understanding of sex-based differences in the prevalence, prognosis, and treatment of diverse chronic liver diseases. Biological sex differences originate principally from sex chromosomes and sex hormones, while gender differences are mainly influenced by sociocultural factors [2]. Although sex/gender differences have tended to be neglected in the approach of precision medicine, they have been extensively studied in recent years. However, there are only few studies on sex differences in chronic liver disease compared to other research areas, such as diabetes mellitus, cardiovascular disease, inflammation, and immunology.

Clinical evidence has suggested that men and women may exhibit marked differences in the epidemiology and natural course of chronic liver disease. Chronic liver disease is the tenth leading cause of death for men (1.8% of deaths) but is not in the top ten for women [3, 4] (Fig. 14.1). Indeed, the liver is the representative, sexually dimorphic, non-reproductive organ with more than 1,000 genes differently expressed between men and women [5]. Therefore, liver damage may result in different clinical consequences between men and women. In this chapter, whether biological sex differences may affect the development and progression of chronic liver disease will be reviewed and summarized.

14.2 Autoimmune Liver Disease

The major forms of autoimmune liver disease are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) [6]. They follow a progressive course that if untreated develops into liver failure requiring liver transplantation [7]. In general, autoimmune diseases are much more common in women than in men, including autoimmune liver

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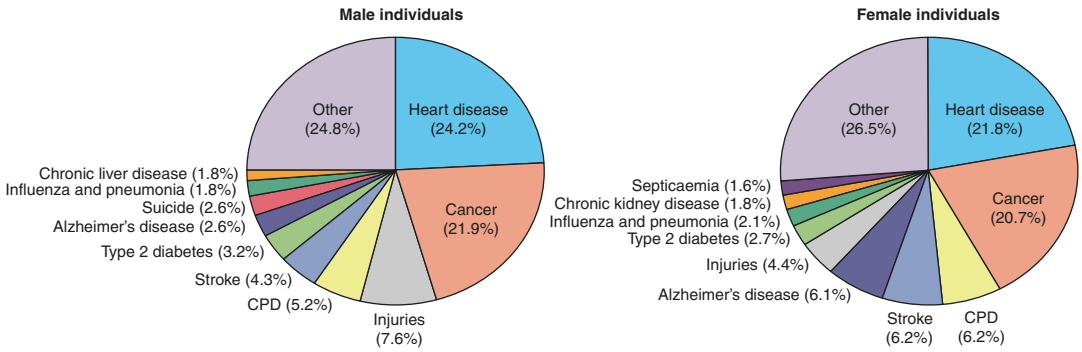

Fig. 14.1 Distribution of the major leading causes of death by sex: USA, 2017 (adapted from Mauvais-Jarvis et al. [4])

diseases. For example, women are ten times more likely to have PBC [8–11] and four times more likely to have AIH [10, 12]. Sex may also have an impact on the clinical course of autoimmune liver diseases and the occurrence of complications, such as hepatocellular carcinoma (HCC). Altogether, there is clear evidence for sex affecting the epidemiology, clinical manifestation, and course of AIH and PBC, while the influence of sex on PSC incidence is much smaller, and its influence on disease course is also less clear. Clearly, additional data on the effect of sex on the progression, comorbidity, and mortality of autoimmune liver diseases are required. Although the pathophysiology of sex differences in autoimmune liver diseases is unknown, several factors, such as genetic predisposition, sex hormones, and environmental factors alone or—more likely—in combination, are thought to play a complex and interactive role in the sex-specific disparity of autoimmune liver diseases. We will discuss how sex-related factors, such as sex hormones [13–15], sex chromosomes [16–20], microbiome [21–24], and environmental factors [25–29], may affect autoimmune liver diseases [30] (Fig. 14.2) and summarize our understanding of how sex influences the pathogenesis, clinical manifestations, and prognosis of autoimmune liver diseases [31–40] (Table 14.1).

14.2.1 Autoimmune Hepatitis

Autoimmune liver diseases are deemed rare diseases; however, a marked increase in incidence and prevalence is observed over time. The prevalence of AIH ranges from 16 to 18 per 100,000 population in Europe, yet prevalence and clinical presentation vary according to ethnicity [31]. A large Danish population-based study assessed the incidence and prevalence of AIH during a 20-year time period. Notably, a marked increase in AIH incidence over time could be observed [41]. AIH is characterized by progressive hepatic inflammation, circulating autoantibodies, hypergammaglobulinemia, and interface hepatitis on liver histology [42]. AIH is highly prevalent in women, representing the 80% of affected patients, with a bimodal age distribution at presentation [31]. An impaired immune reaction of abnormal T lymphocytes to autologous hepatocytes caused by a failure of immunological tolerance is considered the main immunopathogenesis of AIH [43]. AIH is classified as type 1 or 2, based on the nature of serum autoantibodies [12]. Human leukocyte antigen (HLA) DR4 is more prevalent in women than in men with type 1 AIH and has been associated with other concurrent autoimmune disorders and remission during corticosteroid treatment, while HLA DR3 has been associated with early age onset and treatment failure [44, 45]. Czaja et al. [46] analyzed a cohort of 185 well-defined AIH patients and did not find any significant gender-based differences in terms of response to steroid treatment, whereas HLA haplotype (DR3 or DR4) was the only predictor of treatment failure and risk of progression to liver failure or liver transplant in women, with HLA DR3 being associated with treatment failure in both men and women [33]. In another study involving a

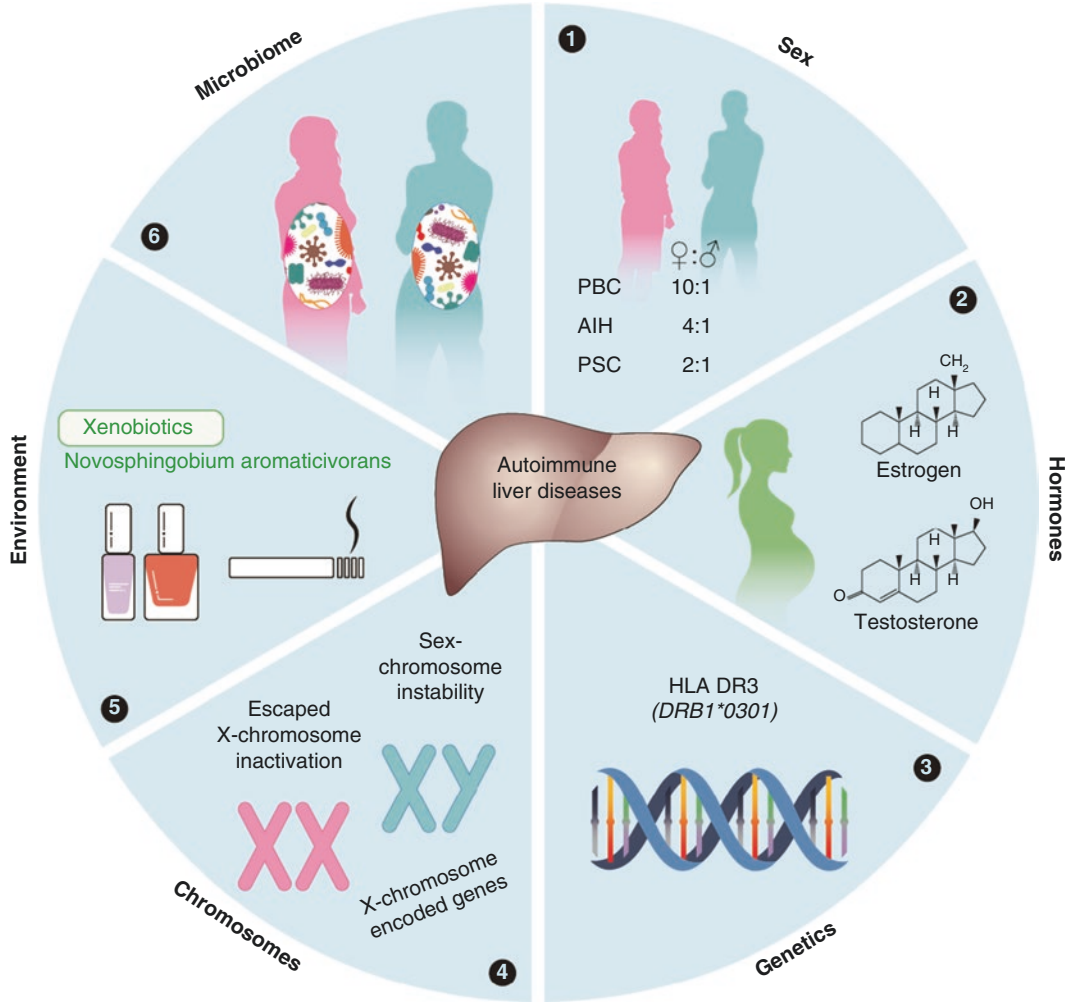

Fig. 14.2 Sex-related pathophysiologic mechanisms in autoimmune liver diseases (adapted from Schwinge and Schramm [30])

European cohort of 238 patients with AIH, males presented at a younger age with a higher relapse rate but had a better long-term outcome than females independent of HLA allotype [32]. The reasons for better survival outcomes in males remain unknown, but they do not appear to reflect differences in either the time to diagnosis, treatment response, treatment regimen, or frequency of relapses between men and women. In a Japanese study evaluating clinical features of male patients with AIH, the frequency of normalization of serum alanine aminotransferase (ALT) level within 6 months after beginning of corticosteroid treatment was significantly lower in men (73%) compared to women (93%) [47]. However, it remains uncertain whether sex (especially, female) confers only a susceptibility to the development of AIH or has an influence on drug response. The severity of AIH in women seems to decrease during the second trimester of pregnancy when estrogen is secreted at high levels, and acute exacerbation occurs after delivery [48]. High level of estrogen seems to be associated with an anti-inflammatory milieu [49].

Table 14.1 Sex differences and sex-related factors in autoimmune liver diseases

AIH	Male	Year (reference)
Prevalence compared to female	25%	2015 [31]
Younger age at onset	↑	2008 [32]
Higher relapse rate	↑	2008 [32]
Frequency of HLA-DR3	↑	1991 [33]
Patient survival	↑	2008 [32]
PBC	Male	Year (reference)
Prevalence compared to females	10%	2012 [34]
Age at diagnosis	↑	2012 [35]
Pruritus, fatigue	↓	2013, 2012 [35, 36]
Concomitant autoimmune diseases	↓	2012 [35]
Jaundice and serum transaminases	↑	2013 [36]
Insufficient UDCA response	↑	2013, 2007 [36, 37]
HCC incidence	↑	1986 [38]
Patient survival	↓	1986 [38]
PSC	Male	Year (reference)
Prevalence compared to females	50–60%	2011 [39]
Prevalence of associated IBD	↑	2011, 2017 [39, 40]
Patient survival	↓	2017 [40]

14.2.2 Primary Biliary Cholangitis

PBC is an autoimmune liver disease that predominantly affects women ten times more often than men [8, 11, 50] and rarely affects children [51]. PBC is characterized by chronic destructive cholangitis, with typical seropositivity for antimitochondrial antibodies [11, 52]. The prevalence and incidence of PBC vary considerably worldwide. The incidence of PBC in European populations ranges from 0.33 to 5.8 per 100,000 population per year with a prevalence reaching 40 per 100,000 population [34]. On the contrary, in the Asia-Pacific region, the prevalence and incidence of PBC appear higher than previously expected, with a pattern of disease diagnosis at a slightly older age (approximately aged around 60 years). A recent systematic review identified 18 studies from 7 Asia-Pacific countries or regions (including Japan, China, New Zealand, South Korea, Australia, India, and Singapore) [53]. The overall prevalence of PBC was 118.8 cases per million (95% CI, 50.0–187.6), with variation from high prevalence in Japan and China to low prevalence in South Korea and Australia. PBC occurs between 40 and 60 years of age [54]. Women with PBC present at a younger age with an increased rate of pruritus and appear to have slower progression rates of fibrosis than men with PBC [35, 55, 56], suggesting that sex hormones are linked to pruritus development and fibrosis progression. In addition, female sex hormones may cause more constitutional symptoms including malaise, anorexia, weight loss, and fatigue. In contrast, men more likely experience jaundice and upper gastrointestinal bleeding [57]. On the contrary, men with PBC tend to be less symptomatic at presentation than women with PBC, which may result in delayed diagnosis [35]. Additionally, fatigue was significantly less marked in men with PBC [36]. Concomitant autoimmune diseases, such as scleroderma and Sicca syndrome, were shown to be less prevalent in men [35]. PBC can progress to cirrhosis and subsequent liver failure, ultimately requiring liver transplantation [58]. Men with PBC presented at an older age and seemed to have a more severe clinical course and higher overall mortality compared to women with PBC [36]. Thus, these data indicate that women are more frequently affected by PBC and more symptomatic but have a better outcome, including better treatment response and less liver-related complications, than men. Although satisfactory reasons to explain the rarity of PBC in men are still lacking, X chromosome monosomy and fetal microchimerism may account for a strong female preponderance observed in PBC [18, 59]. Epigenomic effects are additively important, presumably to modulate the sex selectivity and biliary selectivity of disease and disease expression: one example being the role of microRNAs in the pathogenesis of PBC [60, 61]. Epidemiologic evidence has also suggested different environ-

mental risk factors between men and women, including hair dye use, recurrent urinary tract infection, smoking, and estrogen deficiency, all of which may contribute to the increased susceptibility of women to PBC [59, 62, 63]. However, the incidence rate of HCC was higher in men than in women. Male sex and advanced histological stage independently contributed to the development of HCC [38, 64–68]. The UK-PBC Consortium reported the impacts of sex and age in predicting the prognosis of PBC using a cohort of 2353 non-transplanted PBC patients [36]. Alkaline phosphatase (ALP), which is a marker of disease severity, ALT, and gamma-glutamyl transpeptidase (GGT) levels were higher in men than in women, and men presented at an older age and with a more severe disease, and male sex was an independent risk factor for non-response to ursodeoxycholic acid (UDCA) [36, 37]. Moreover, female sex revealed a clear age-related difference in response to UDCA: women presenting younger than the age of 45 were significantly less likely to respond to UDCA than either men or elder women at presentation, with age being an independent predictor of UDCA response. Yagi et al. [69] reported a Japanese-based multicenter, observational, cross-sectional study in which female sex, a younger age at diagnosis (<50 years), and a lower concentration of serum albumin were independently associated with measures of fatigue, whereas a longer follow-up period and lower concentrations of serum albumin were associated with the burden of itch. Thus, baseline characteristics, such as young age, male sex, and advanced disease, and serum markers of liver injury, particularly bilirubin and ALP, are used to stratify the risk of developing complications of end-stage liver disease and assess treatment responsiveness. For patients who do not sufficiently respond to UDCA, or those with UDCA intolerance, conditionally licensed add-on therapy is with the farnesoid X receptor agonist, obeticholic acid [70–73]. Off-label therapy is recognized as an alternative, notably with a pan-peroxisome proliferator-activated receptor agonist, bezafibrate [74–76].

14.2.3 Primary Sclerosing Cholangitis

PSC is a chronic cholestatic liver disease characterized by progressive inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts [77], leading to cholestasis, progressive hepatic fibrosis, and eventually decompensated cirrhosis [78, 79]. In contrast to PBC and AIH, PSC is an autoimmune disease with atypical features including an almost equal male-to-female ratio, the absence of disease-specific autoantibodies, and poor response to immunosuppression [80, 81]. The incidence of PSC was 1.25 per 100,000 population per year in men and 0.54 per 100,000 population per year in women [79]. The prevalence of PSC in Europeans is estimated to be 10 per 100,000 population. Women are less likely to have PSC than men (M > F, 7:3) [80, 82, 83]. The pathogenesis of PSC remains uncertain because it is a complex immune-mediated disease. The most accredited theory is that in genetically predisposed individuals, the environmental exposure to infective agents or toxins causes persistent immune-mediated damage to cholangiocytes and progressive destruction of bile ducts, leading to chronic cholestasis [77, 84]. Survival outcome is severely impaired by the high risk of developing cholangiocarcinoma [40, 85]. Sex is not an independent risk factor for mortality in PSC, although one study found that cholangiocarcinoma was more common in men [78, 86]. There are an almost equal sex distribution and no significant differences in age at diagnosis between men and women with PSC [39]. However, data related to sex differences in PSC severity are scarce. A recent retrospective outcome analysis reported that men with classical PSC showed a slight, albeit statistically significant, increased risk of disease progression when compared to women with a matched phenotype [40]. Likewise, associated inflammatory bowel diseases were found more frequently in men than in women with PSC [40]. Currently, there is no established medical treatment with a proven benefit for PSC patients [87]. Only liver transplantation represents the

treatment of choice in advanced stages of PSC [88, 89]. Notably, PSC recurs in as much as 20–30% of patients within 5 years of liver transplantation [90].

14.3 Alcohol-Related Liver Disease

Alcohol-related liver disease is becoming increasingly prevalent worldwide. Women are more susceptible than men to the adverse effects of alcohol. Women develop alcohol-related liver disease even after a shorter period and smaller amounts of alcohol intake than men, and liver injury progresses more rapidly and severely in women than in men [91]. The exact mechanisms that make sex differences in the incidence, natural course, and prognosis of alcohol-related liver diseases are not completely understood. Alcohol affects women's bodies differently than men's bodies not just because women typically weigh less than men. For example, women generally have less water and more fat in their bodies than men, causing the proportional level of alcohol in the blood to be higher [92]. To date, no single factor can account for this increased female susceptibility to alcoholic liver damage. Lower gastric mucosal alcohol dehydrogenase (ADH) content in women has been suggested to possibly lead to less first-pass clearance of alcohol in the stomach [93]. Hormonal influence on the metabolism of alcohol or a higher prevalence of immunologic abnormalities is likely responsible for the differences in the prevalence of alcoholic liver damage between men and women. A sex hormone, estrogen, also impacts on hepatic ADH activity and Kupffer cell inflammatory response to gut microbiota translocation and metabolic pathways [94–98]. Therefore, sex difference observed in patients with alcohol-related liver disease is caused by the susceptibility of females to liver damage from smaller quantities of ethanol. While men are more likely to experience alcohol-related liver disease due to a higher rate of alcohol use disorder, women with alcohol-related liver disease show more rapid progression of fibrosis in the liver. Women are also drinking more than before, increasing concerns about alcohol-related liver diseases [99]. A recent 2017 report showed a nearly 84% jump in alcohol use disorders among women from 2001 to 2012, compared to a 35% increase for men [100]. During the coronavirus disease-2019 (COVID-19) pandemic, a national survey found significant increases in heavy drinking and alcohol-related problems for women [101]. We will discuss an increasing prevalence of alcohol-related liver disease in women, putative mechanisms of sex-specific differences in alcohol metabolism that may account for this discrepancy between the sexes, and sex differences in the management of alcohol-related liver disease. Better understanding of the changing epidemiology and basic mechanisms underlying sex differences during the development of alcohol-related liver disease may contribute to the improved prevention and treatment for women who represent a rapidly growing subset of patients with alcohol-related liver disease.

14.3.1 Epidemiology of Alcohol Consumption and Alcohol-Related Liver Disease by Sex

Alcohol use disorder is highly prevalent in the United States as well as Korea and causes significant morbidity and mortality [99]. In Korea, women's monthly drinking rate and high-risk drinking rate are gradually increasing [102] (Fig. 14.3). Six different national surveys conducted between 2000 and 2016 found that the number of women ≥18 years who drink each year rose about 0.6% each year, and the number who binge drink increased as well, while there were no increases in men [103]. Alcohol-related liver disease is second to nonalcoholic fatty liver disease (United States) or chronic hepatitis B virus (HBV) infection (Korea) as the leading cause of cirrhosis. In addition, alcohol-related liver disease is the third most common cause of HCC in Korea. A lifetime prevalence of severe alcohol use disorder in the United States is 18.3% of men and 9.7% of women, respectively [104]. In general, men have significantly higher rates of

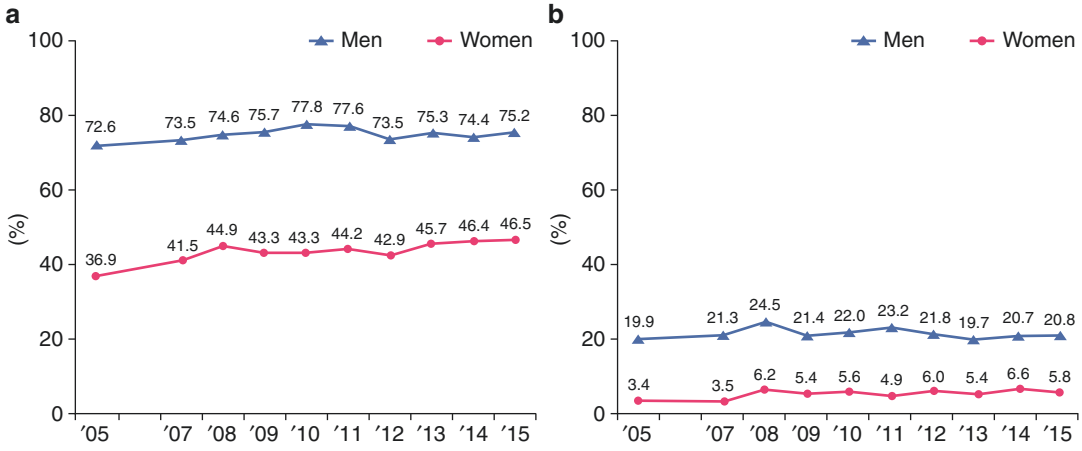

Fig. 14.3 Monthly alcohol drinking rates (**a**) and high-risk alcohol drinking rates (**b**) (2016 Korea National Health and Nutrition Examination Survey (KNHANES) data) (adapted from Jang et al. [102])

alcohol consumption and high-volume drinking compared to women [105]. Men have been shown to exceed women in drinking quantity, frequency, and the rate of binge drinking; and this pattern has been consistently demonstrated throughout the world and across different cultures [106]. Women who previously drank large amounts of alcohol are more likely to stop drinking than men. The magnitudes of these sex differences vary across different cultures, indicating the multifactorial nature of alcohol consumption and drinking behavior [107]. The overall mortality from alcohol-related liver disease in the United States has increased since 2006 in every age group and race, with the exception of non-Hispanic Black men [108]. In addition, premature deaths from overall chronic liver disease and cirrhosis are expected to rise for all racial and ethnic groups except Black men until 2030 [109]. Despite the increasing overall prevalence of alcohol consumption, women are likely to develop alcohol-related liver disease with lesser alcohol exposure and suffer worse outcomes as compared with men. A systematic review and meta-analysis demonstrated that consumption of 1 ~ 2 drinks per day as compared with long-term alcohol abstinence was associated with an increased risk of liver cirrhosis in women, but not in men. Moreover, the risk for developing cirrhosis was consistently higher in women than in men for all levels of alcohol consumption [110]. Also, younger patients admitted with alcohol-related liver disease and acute-on-chronic liver failure were more likely to be Hispanic, obese, and women [111]. The total number of hospitalizations in patients with alcoholic cirrhosis increased by 19.8% from 2007 to 2014; this increase was more prominent in women who had an increased hospitalization rate by 33.5% as compared with an increase of only 14.7% in hospitalizations seen in men with alcoholic cirrhosis [112]. There appears to be sex-specific differences in liver-related outcomes in patients who achieve sobriety. A study of patients with histologically confirmed alcoholic hepatitis in the absence of cirrhosis demonstrated that four of seven women who abstained from alcohol developed cirrhosis within 1–2 years compared with zero of six men [113]. This study suggests that women may have accelerated histological progression despite sobriety compared to men. Alcohol-related liver disease poses a significant opportunity for intervention in the prevention and treatment of chronic liver disease. Women represent a growing subset of alcohol-related liver disease patient population; and sex differences in the trends in alcohol consumption and liver disease development or progression are important aspects of understanding the worse trajectory that women tend to have as compared with men. Despite the higher prevalence of alcohol consumption in men than in women, women are more commonly affected by

alcohol-induced liver injury [114]. The liver is the primary organ of alcohol metabolism and as such is the main site of injury in patients with excessive alcohol consumption. Alcohol-related liver diseases include alcohol-related steatosis, hepatitis, steatohepatitis, fibrosis, cirrhosis, and HCC. In a prospective study of alcohol use in Denmark, among people who consumed ≥4 alcoholic drinks per day, women had a relative risk of 17.0 for alcohol-related cirrhosis compared to a relative risk of 7.0 in men [115] (Fig. 14.4). This study also found that for any given level of alcohol intake, women had a higher relative risk of developing alcohol-related liver disease and alcohol-related cirrhosis compared with men [115]. A retrospective study of alcohol-related liver disease demonstrated that women showed a significantly more rapid progression to cirrhosis (20 years on average) as compared with the rate of progression to cirrhosis in men (35 years on average) [56]. In a study of alcohol relapse after recovery from severe alcoholic hepatitis, 17% of patients experienced relapsing severe alcoholic hepatitis, and there was a slight trend toward recurrence being more common in females, which was not statistically significant [116]. Despite the sex-specific differences in the development and progression of alcohol-related liver disease, it remains uncertain whether there is a survival difference between men and women with alcohol-related liver disease. In a large US trial that reported alcohol and tobacco use, mortality from alcohol-related liver disease was not significantly different between the sexes for those consuming 2 ~ 3 drinks per day. However, mortality increased in men who consumed ≥4 drinks per day compared with women [114, 117]. Although men have higher death rates, the gap between death rates of men and women is narrowing. This is especially true of women who are 25–34 years of age, and the number of non-Hispanic White women dying from ALD grows more rapidly compared to rates for non-Hispanic Black women [118]. In a recent US National Health and Nutrition Examination Survey, alcohol-induced acute on chronic liver failure occurred more frequently in young, female, and Hispanic patients with alcohol-related liver disease [119].

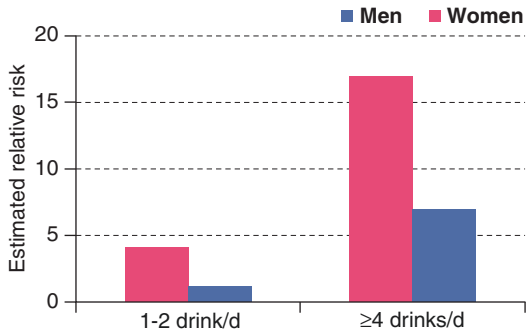

Fig. 14.4 The estimated relative risk of alcohol-related cirrhosis in men and women according to alcohol intake amounts (modified from Becker et al. [115])

14.3.2 Putative Mechanisms of Sex Differences in Alcohol-Related Liver Disease

Alcohol-induced liver injury is instigated by ethanol metabolism via ADH and cytochrome P450 2E1 pathways that produce hepatotoxic acetaldehydes. There are sex differences acknowledged in the pharmacokinetics of alcohol [120] (see Sect. 2.4.1). For equal alcohol intake, women develop higher blood alcohol concentrations as compared with men [121]. Women are generally smaller than men; therefore, the same alcohol consumption results in higher serum alcohol concentrations in women as compared with men. In addition, women have smaller body water content per kg of body weight as compared with men, leading to a smaller volume of distribution. Table 14.2 summarizes sex-specific differences in alcohol metabolism and its contribution to sex differences in alcohol-related liver disease. A number of studies have shown a difference in gastric ADH activities between women and men [93]. The metabolism of alcohol by gastric ADH decreases its systemic bioavailability. Therefore, the stomach protects against systemic absorption of alcohol via ADH activity. Women have increased bioavailability of alcohol due to decreased first-pass metabolism, leading to increased susceptibility to alcohol-related liver

Table 14.2 Mechanisms for sex differences in alcohol-related liver disease

Mechanism	Sex difference	Outcome
Ethanol metabolism	Women typically have decreased body weight Women have decreased body water	Decreased volume of distribution of alcohol and increased blood alcohol concentration in women
First-pass effect	Women have decreased gastric ADH Women have slower gastric emptying of alcohol	Increased bioavailability of alcohol in women
Estrogen	Chronic alcohol consumption increases estrogen in male and female rodent models	Increased estrogen coincides with more significant liver injury in rodent models
Growth hormone	Female rodent models show continuous secretion of GH which leads to increased hepatic ADH activity	Increased accumulation of toxic acetaldehyde
Kupffer cell activation by endotoxin	Estrogen sensitizes Kupffer cells to LPS in rodent models	Increased accumulation of pro-inflammatory cytokines

ADH alcohol dehydrogenase, *GH* growth hormone, *LPS* lipopolysaccharide

disease [93]. Women thereby have less first-pass metabolism than men, which is associated with significantly lower activity of gastric ADH in women as compared with men [121]. In addition, gastric emptying of alcohol is 42% slower in women, and hepatic oxidation is 10% higher in women. Altogether, decreased gastric metabolism in women due to significantly less active gastric ADH primarily accounts for sex differences in serum alcohol levels [121]. Sex differences in gastric ADH activity are amplified in patients who have undergone gastric bypass surgery, wherein gastric ADH is circumvented, contributing to increased risk of alcohol-related liver disease associated with first-pass metabolism [122]. Cytochrome P450 2E1 related to ethanol metabolism increases in activity when administered with ethanol, which can be confirmed in female rats since this increase in activity is reduced by the administration of anti-estrogen [123]. Considering that cytochrome P450 is regulated by growth hormone and sex hormone, the differences in these hormones between the sexes appear to induce the difference in the expression of cytochrome P450 between men and women, leading to an increase in toxic metabolites and susceptibility to liver damage in women [124]. Although the initial absorption and metabolism of alcohol differ between the sexes, there are additional mechanisms at the level of the liver that further contribute to sex differences in alcohol-induced liver injury. Chronic alcohol intake alters hormone expression in both sexes. Not only is the liver the site of steroid hormone metabolism, but also it is responsive to sex hormones, and as such there is ongoing research being done to further characterize the role of hormones in alcohol-related liver disease [125]. Estrogen modulates glucose/lipid metabolism and hepatic steatosis/inflammation via estrogen receptors (ERs) on hepatocytes [126]. An experimental rat model demonstrated that alcohol increases ER expression in male rat livers, resulting in hepatocellular proliferation. This was in contrast to female rat livers wherein alcohol did not increase ER expression and thus hepatocellular apoptosis predominated over hepatocellular proliferation [97]. Additional studies showed that with chronic alcohol exposure, androgen-responsive functions in the male rat liver decrease and, subsequently, testosterone levels decrease and estrogen levels increase due to changes in hepatic estrogen metabolism [125, 127]. Taken together, most significant liver injury occurred under the influence of high estrogen and low testosterone levels. Indeed, postmenopausal women with chronic alcohol consumption had approximately twofold higher estrogen levels [125]. Additional studies are warranted to further evaluate the clinical impact of alcohol on hormone metabolism in men and women. Estrogen stimulates the secretion of growth hormone [128]. In rodent models of growth hormone secretion showing sex differences, female rats show continuous secretion of growth hormone contrary to

pulsatile secretion in male rats [129]. Growth hormone increases hepatic ADH activity, and subsequently, hepatic ADH activity is higher in female rodents compared with male rodents [94]. This increased hepatic ADH activity in females leads to increased accumulation of toxic acetaldehyde, conferring the increased susceptibility of females to alcohol-related liver disease. Estrogen and alcohol seem to produce intrahepatic inflammation through interactions with each other; it is well known that alcohol intake causes liver damage due to gut barrier disruption, bacterial translocation from the gut to portal vein, and increased endotoxins. Kupffer cells are able to remove endotoxins (i.e., lipopolysaccharides) with Kupffer cell activation and pro-inflammatory cytokine secretion [96, 130]. In rat experiments, when estrogen was administered after ethanol intake, estrogen increased the sensitivity of Kupffer cells to endotoxin [95, 96], blood level of endotoxin, and tumor necrosis factor-alpha (TNF-α) production by Kupffer cells, which eventually led to an increase in intrahepatic inflammation [97, 98]. This study suggested that estrogen sensitizes Kupffer cells to endotoxin, resulting in an increased toxic mediator production.

14.3.3 Sex Differences in the Management of Alcohol-Related Liver Disease

Although there are significant differences between the sexes in alcohol metabolism and the development and severity of alcohol-related liver disease, alcohol abstinence is the cornerstone of treatment in both men and women. This highlights the significance of identifying patients with or at risk of alcohol abuse and providing them with effective therapeutic options. Men with alcohol-related liver disease were more likely to be listed and transplanted compared to women with alcohol-related liver disease. While men with alcohol-related liver disease had more lifetime substance use and related consequences, women had more psychiatric comorbidities and were less likely to be listed due to active alcohol and opioid use. Early detection and effective treatment of psychiatric and substance use disorders in women with alcohol-related liver disease may improve their transplant eligibility [131].

14.4 Viral Hepatitis

HBV and hepatitis C virus (HCV) are different hepatotropic viruses in the context of genomic structure, life cycle, and immunopathogenesis. Furthermore, the incidence of HBV or HCV infection is higher in males compared to females, presenting a faster disease progression with worse overall survival outcomes. Indeed, women are in general better protected against viral infections and show a lower risk of death from malignant cancer as compared to men. Sex contributes to shape immune responses, producing significant differences in the immunopathogenesis of viral hepatitis between the sexes. Females usually develop stronger innate and adaptive immune responses to viral infections than males. In addition, sex hormones differentially affect the immune responses to HBV and HCV by specific binding to sex hormone receptors on the immune cells. For example, estrogen has an immune-stimulating effect, whereas androgen has an immune-suppressing effect. However, androgen can also directly interact with HBV genome integrated into the hepatocyte nucleus and activate transcription of HBV oncoproteins. On the contrary, estradiol and ERs protect hepatocytes from inflammation, apoptosis, and oxidative stress that contribute to fibrosis and malignant transformation. In HCV-related cirrhosis and HCC, the decreased expression of ERα in male patients may be responsible for the worse outcomes of HCV infection in men. The synergistic effect of sex hormones and sexually dimorphic immune responses on the immunopathogenesis of HBV/HCV infections may account for the sex disparity in the clinical outcomes and progression of viral hepatitis. Herein, we will discuss underlying mechanisms that are considered for the noticed sex-related differences in HBV/HCV infections. A better appreciation of these differences between the sexes may be useful for improving

sex-specific treatment options in patients with viral hepatitis.

14.4.1 Chronic Hepatitis B

The sex difference in chronic HBV infection has been perceived for a long time [132]. Indeed, female HBV carriers have lower viral loads than male carriers [133, 134], and the prevalence of serum HBV surface antigen (HBsAg) has been reported to be higher in men than in women [135]. Some differences have been attributed to sex hormone effects directly by regulating HBV transcription, entry, and integration and indirectly by modulating the immune response to HBV infection. According to the mouse models of HBV infection, sex-related disparities in the adaptive immune response to HBV infection may be explained by different $CD8^+$ T-cell activity. Higher $CD8^+$ T-cell activity and a lower number of intrahepatic regulatory T cells were observed in females than in males [136]. However, the roles of androgen and estrogen in regulating T-cell response to HBV infection remain unclear. Susceptibility to HBV infection is associated with a particular ERα polymorphism; this polymorphism affects *ESR1* gene transcription, with the defective response of immune cells to estrogens [137]. A single nucleotide polymorphism in the gene for ERα associated with persistent HBV infection may illustrate the influence of sex hormones on the HBV-specific immune response [138]. Given the known effect of sex hormones on the immune system, this may account for the sex-based different susceptibility to HBV infection. Besides their effect on immune responses, sex hormones also directly influence viral activity. Resultingly, the viral loads and outcomes of several viral infections are different between the sexes [139–145]. Estrogen can suppress hepatic fibrogenesis [146], work as an endogenous antioxidant by reducing reactive oxidant species [147], and modulate cytokine production to protect females from liver inflammation [148]. One of the molecular mechanisms underlying the difference in the outcome of HBV infection between the sexes is direct binding of the ER and androgen receptor to binding sites within HBV enhancer I [149]. In contrast, the androgen receptor can bind directly to a specific response element within HBV enhancer I and increase overall HBV transcription [150]. In addition, estrogen also influences viral entry. Indeed, estradiol represses the expression of the major HBV entry receptor sodium taurocholate cotransporting polypeptide (NTCP) in hepatocytes through ERα, thus inhibits viral entry, and restricts infection in the liver [151, 152]. Sex hormones play a crucial role in the regulation of immune responses to HBV. This is evidenced by the fact that HBV vaccine exhibits not only higher antibody titers but also stronger adverse effects in young females receiving active immunization [153]. Furthermore, HBsAg and HBeAg seroconversions occur more frequently in females rather than in males [154]. Additionally, androgen exerts an immunosuppressive effect on the development and activation of T cells [155]. Nevertheless, the overall impact of sex hormones on HBV-specific immunity is not completely characterized [156, 157].

14.4.2 Chronic Hepatitis C

Similar to HBV infection, HCV infection is more prevalent in men than in women, with a male-to-female ratio of nearly 2:1 [158]. HCV infection is a disease that disproportionately affects men more than women. Women are more likely to clear the HCV spontaneously. HCV-related fibrosis progression to cirrhosis is more rapid and more common in men than in women if they become chronically infected [159]. In addition to host interleukin 28B (IL-28B) genotype and HCV genotype [160], female sex has also been reported to be an independent predictor of spontaneous resolution from acute HCV infection [161, 162]. Chronic infection will develop in about 70–80% of men and ~ 60% of women [163, 164]. Clearance of infection and disease progression rely on sex [165–168]. Differences in disease progression between the sexes are assumed to be linked to the protective effect of estrogen. Moreover, the rate of disease progression changes

during lifetime in women. Postmenopausal women show more rapid progression of liver fibrosis [169] and poor response to interferon-based antiviral therapy [170]. Liver expresses ERα and ERβ that are responsive to the estrogenic stimulus; however, normal male liver has higher expression of ERα as compared to normal female liver. In contrast, in HCV-related cirrhosis, ERα level has been reported to decrease only in men, suggesting the worse outcome of chronic HCV infection in men than in women [171]. The worse outcome of HCV infection in men may also be explained by the direct influence of sex hormones on HCV itself. 17β-Estradiol was found to inhibit the production of mature HCV virions via ERα binding [172, 173] and to inhibit HCV entry via downregulation of occludin in infected cell cultures [174]. So far, studies analyzing the effect of testosterone on HCV replication are lacking. The effect of estrogen and testosterone on HCV replication may explain the lower incidence of HCV infection and slower progression of liver disease in premenopausal women than in postmenopausal women and men. Furthermore, alcohol consumption may also contribute to chronic hepatitis progression as men are more likely to engage in heavy drinking [105, 175]. Sex differences in treatment-induced clearance of HCV have also been reported. A randomized study reported an increased and sustained clearance of HCV from the bloodstream (i.e., sustained virological response, SVR) in women after treatment with pegylated interferon and ribavirin [176]. Women may also achieve a higher SVR rate with higher doses of peginterferon [177]. In young women of reproductive age, the combined treatment of peginterferon and ribavirin achieves SVR with a nearly 100% chance [178]. In contrast, early menopause is associated with a poor response to interferon-based antiviral therapy, highlighting a role of estrogen in this setting [179]. The addition of raloxifene, an oral selective ER modulator, to peginterferon and ribavirin significantly improves the SVR rate in the treatment of postmenopausal women, but this approach became meaningless due to the development of oral direct-acting antiviral agents (DAAs) [180]. In the current era of DAAs, demographic factors, including sex differences, have lost their significant role in antiviral treatment response, since the treatment outcome has remarkably improved owing to the recent advance of DAA treatment.

14.5 Conclusions

Sex difference medicine focuses on understanding the clinical, pathophysiological, therapeutic, and preventive differences in various medical diseases that are equally represented in men and women. The ultimate goal of this field is to provide the best treatment to each individual man and woman based on scientific evidence. Sex disparities in incidence, presentation, natural history, and outcomes clearly exist for various chronic liver diseases. To date, basic and clinical research has been gender- and sex-unbalanced, with female subjects generally underrepresented. Therefore, a special attention on more sex-specific approaches to hepatology and general medicine is required, and additional efforts of the research community should be attempted toward a better understanding of the exact mechanisms underlying such sex differences, centered on differing behavioral, hormonal, and immunological factors. Further studies on chronic liver disease mechanisms based on sex differences would offer more efficient, sex-tailored precision medicine.

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Hepatocellular Carcinoma

15

Won Kim

15.1 Introduction

Hepatocellular carcinoma (HCC) prevalence and incidence vary considerably by age, sex, and race/ethnicity. In particular, sex-related variations in HCC have been frequently found in mammals ranging from rodents to humans and were first described in mice in the late 1930s, with female mice being resistant to HCC [1]. The comparative studies have identified that a marked feature of HCC is that males have a higher incidence and worse prognosis compared with females [2]. The striking sex difference implies an important role of sex hormones in the pathogenesis of HCC [3]. The sex difference of HCC has revealed that a ratio of estrogen and testosterone levels may be associated with the development and progression of HCC, suggesting that estrogen- and androgen-mediated signaling pathways may regulate the risk of HCC [4, 5]. Recently, increasing attention has been focused on the genetic alterations of sex chromosomes, which may account for the sex difference of HCC [6–8]. Substantial efforts have been exerted in exploring the molecular mechanisms involved in the sex difference of HCC [4, 5, 8]. In this chapter, we will discuss sex differences in the clinical outcomes and molecular pathobiology of HCC, such as sex hormones, including androgen and estrogen and their receptors, as well as sex chromosomes in the pathogenesis of HCC.

15.2 Clinical Sex Differences in Hepatocellular Carcinoma

HCC has been reported more frequently in men than in women with a male-to-female incidence ratio of 3:1, and this discrepancy is also observed in mice models [4, 9]. Although the biological grounds underlying this sex disparity in the prevalence of HCC are incompletely understood, the disparities in sex distribution are thought to be due to variations in viral hepatitis carrier states, exposure to environmental toxins, or potentially protective effects of estrogen mediated through inhibition of interleukin 6 (IL-6) [4]. Male sex is an independent risk factor for poor outcome of HCC, and females are more likely to be amenable to curative resection or transplantation [10]. Hepatitis B virus (HBV)-related HCC prevalence is much higher in men than in women, and a male-to-female ratio for patients with HBV-related HCC has been reported to be even higher than that of patients with hepatitis C virus (HCV)-related HCC [11]. This effect might be explained

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by regional characteristics (e.g., a higher prevalence of HBV and HCV infection among men). Sexual dimorphisms in metabolism are well acknowledged [12–14] and partly account for sex differences in HCC risk. Several other risk factors for HCC have been suggested for an interaction with sex. Obesity has been associated with a higher risk of HCC in men than in women, especially in non-Asians [15]. A recent study demonstrated a different relationship between body mass index and HCC risk according to sex, with a U-shaped and a linear curve for men and women, respectively [16]. A stronger risk association between diabetes mellitus and HCC has also been reported in men than in women [16–18]. In addition, men are more prone to acquire HBV and HCV infections and develop chronic hepatitis, cirrhosis, and HCC than women [19]. Recent epidemiological studies have demonstrated that compared to men, women with HCC presented with older age, higher frequency of nonalcoholic fatty liver disease, non-cirrhotic HCC, less-advanced stage, and lower frequency of alcohol-related liver disease [20–22]. Previous studies regarding sex disparities in survival rates have yielded conflicting results. Two recent studies reported higher overall survival rates among women after adjusting for confounding factors [20, 21]. Consistently, one of these demonstrated that female sex was independently associated with early HCC detection and response to initial treatment [20]. Conversely, other studies found no sex differences in the prognosis of HCC [22, 23], whereas Asian studies did [24–27]. Another study showed age, sex, and ethnicity interaction in survival rates; women had higher survival rates from HCC than men <55 years, while after 65 years or among Hispanics, there was no survival difference between sexes [27]. A similar interplay between age and sex in HCC survival and further possible age, sex, and race/ethnicity interaction in HCC survival were also found [28]. Future studies with consideration of these interactions are warranted to reconcile this inconsistency between studies.

15.3 Sex Disparity in Hepatocellular Carcinoma Pathobiology

Sex differences are well recognized in cancer mechanisms [29]. Compared to females, males are more susceptible to oxidative stress due to higher NADPH oxidase activity, lower nuclear factor erythroid 2-related factor 2 (NRF2), and lower anti-oxidants [30–32] and have higher induction of IL-6 by Kupffer cells under liver injury [4]. Contrarily, higher physiological estrogen levels protect females from HCC development via the anti-oxidative effect of estrogen [30, 32], anti-fibrotic effect [13], and inhibitory effect on IL-6 production by Kupffer cells [4]. Antiviral immune response modulation by sex hormones may also contribute to explain HCC prevalence in male gender. Estrogens transcriptionally inhibit IL-6, through reduction of MyD88-dependent induction of NF-κB [4, 33]. The protective effect of estrogen is lost after menopause, which may account for the fact that male predominance in HCC incidence attenuates with aging [34]. A higher serotonin synthesis and accumulation in male zebrafish resulted in increased activation of hepatic stellate cells and transforming growth factor β1 expression, which has contributed to the accelerated progression of HCC in male zebrafish with activated *Kras* oncogene expression [35]. Gut microbiota also exhibits sex differences in HCC [36–39]. In an experimental mouse model, higher hepatic hydrophobic bile acid levels were noticed in males, which was associated with a decreased expression of tumor-suppressive microRNA (miR) in the liver and increased incidence of HCC [39]. In addition, similar sex differences in bile acid profiles also exist in humans [38], suggesting that sex differences in gut microbiota and bile acid profiles may contribute to male predominance in the development of HCC. Sex disparities in HCC pathobiology have extensively been explored in functional signatures of differentially expressed genes [40, 41], expression quantitative trait loci [42], and cancer-related driver

genes [42]. These studies demonstrated that HCC in men and women are biologically distinct and may respond differently to anti-cancer treatments.

15.4 Sex Hormones in Hepatocellular Carcinoma Pathobiology

Women's resistance to HCC can be largely explained by the effect of sex hormones, as evidenced by an exceptional increase in HCC incidence in postmenopausal women. Of note, sex-related hormones, such as androgen, progesterone, and estrogen, play an important role in HCC development. Both androgen and estrogen are able to induce hepatocellular adenoma, ultimately leading to HCC development even in individuals without underlying liver disease. HCC tumor tissues express estrogen receptors (ERs), although the clinical significance remains debatable [43, 44]. Normal liver expresses both ERα and ERβ and is responsive to estrogenic stimulus; however, normal male livers have higher expression of ERα compared to normal female livers. Contrarily, in HCV-related HCC, ERα level has been decreased only in male patients compared to normal male livers [45]. The effect of sex hormones on HCC development is mainly thought to occur on the DNA level, since lipid-soluble sex hormones enter the plasma membrane and interact with intracellular receptors. Androgen receptor (AR) and ERα act in an antagonistic manner through differential regulation of gene expression. A central role for the transcription factors Foxa1/Foxa2 in controlling estrogen and androgen signaling was proposed [46]. Estrogens may act as a suppressor of HCC by reducing production of IL-6 [4]. In fact, ablation of IL-6 abolishes sex differences in hepatocarcinogenesis in mice, and IL-6 has been reported to be a target of the Foxa transcription factor [47]. Estrogens can exert both tumorigenic and anti-tumorigenic properties. Androgens contribute to HCC development as a tumor promoter by upregulation of β-catenin/T-cell factor signaling and via induction of oxidative stress and DNA damage [4, 48, 49]. Several studies have evaluated the anti-tumor effect of antiestrogen therapy in patients with HCC. Since ERs are present in one third of HCCs and estrogen-dependent HCC growth has been shown in experimental models, HCC could potentially benefit from ER blockage. However, tamoxifen treatment in patients with advanced HCC has failed to show survival benefit [50–52]. As tamoxifen is the inhibitor of p-glycoprotein, a multidrug resistance gene protein, addition of tamoxifen to chemotherapy has also failed to show any survival benefit [50, 53]. Megestrol, a progestin with progestogenic and weak partial androgenic activity, has even shown a trend toward worse survival [53].

15.5 Sex Chromosomes in Hepatocellular Carcinoma Pathobiology

Genetic alterations of chromosomes X and Y are frequently found in patients with HCC, including chromosome-specific gene change, oncogene or tumor suppressor gene expression, and structural rearrangements of chromosomes [7, 8, 54]. This suggests that genes located on sex chromosomes may be responsible for HCC [55, 56]. A large body of evidence has shown direct involvement of X chromosome-encoded genes in cancer development. The X chromosome is highly enriched in immune-related genes including several X-linked miRs located within an estrogen response element. Alterations in the Y chromosome are also frequently found in malignancies. Loss of Y chromosome has been reported for several cancers, although whether this is a cause or consequence of malignant transformation remains unclear. In particular, sex-determining region Y (SRY) expression confers malignant properties in HCC [57]. SRY upregulates *Sgf29* gene expression and thus suppresses c-Myc-mediated malignant transformation. Moreover, SRY expression induces multiple stem cell factors, and ablation of SRY can suppress HCC

development [58]. Testis-specific Y-encoded protein 1 (TSPY) is a Y-linked gene that has a significant effect on HCC development [59]. TSPY is encoded by the Y chromosome and co-expressed with AR in HCC cells. Therefore, a crosstalk between AR and TSPY is implicated in male hepatocarcinogenesis [60]. TSPY is an oncogene with well-known functions in germ cell differentiation, mitosis, and meiosis [61] and promotes cell proliferation and oncogenesis, whereas its X-located homolog, TSPY homolog X (TSPX), retards cell cycle and oncogenic progression. TSPX promotes proteasomal degradation of HBV-encoded X oncoprotein and has been suggested as a tumor suppressor in HBV-related HCC [62]. Lastly, RNA-binding motif protein (RBMY) has been suggested as a candidate oncogene specific for male HCC [63] and, similar to TSPY, seems to be involved in the regulation of AR activity and contributes to male predominance in the development of HCC [64].

15.6 Conclusions

HCC is characterized by an obvious sex disparity, although it lacks an exact mechanistic basis. This chapter recapitulated recent research investigating the role of sex hormones and sex chromosomes in this sex-specific hepatocarcinogenesis. Sex hormones and their corresponding receptors comprise two tumor-promoting and inhibiting signaling pathways through different networks. Genetic alterations in sex chromosomes may also contribute to the exact mechanism underlying sex disparity in the development and progression of HCC. In brief, sex disparity in HCC is attributed to multiple mechanisms, and simultaneous targeting of both sex hormones and sex chromosomes may be a novel and promising therapeutic strategy against HCC. Further mechanistic understanding of sex differences in hepatocarcinogenesis, along with epidemiological characterization and incorporation of reproductive history, would enable accurate risk stratification and personalized therapeutic approaches.

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Part VIII

Colon

Irritable Bowel Syndrome

16

Nayoung Kim

16.1 Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder (FGID) characterized by repeated changes in the form of stool or defecation habits with abdominal pain or discomfort without organic diseases. IBS is a common disorder, with a prevalence of 7–24% among women and 5–19% among men (i.e., IBS is more common among women) [1–3]. IBS is one of the most common reasons for visits to primary healthcare facilities, and patients with IBS commonly present with symptoms unrelated to the digestive system such as migraine and fibromyalgia [4, 5]. The symptoms of IBS occur irregularly, can vary depending on time, and demonstrate a considerable degree of variation, as overlap syndrome where IBS presents with other functional disorders is common. Therefore, a more objective diagnosis needs to be made, and patients can be categorized into more homogeneous groups by using internationally developed diagnostic criteria. Various diagnostic criteria approved internationally have been used, and the Rome IV diagnostic criteria (2016), which are a revised version of the Rome III diagnostic criteria (2006), currently constitute the most commonly used diagnostic framework [6]. IBS is the first FGID to which the concept of sex/gender-specific medicine has been applied not only because it is more common among women but also because IBS in female patients is influenced more by the brain-gut axis. IBS with predominant constipation (IBS-C) is more common among women, and they have more severe symptoms [7]. In contrast, postinfectious IBS or IBS with predominant diarrhea (IBS-D) is more common among male patients. This review aims to provide the sex/gender differences in the epidemiology, mechanism, symptoms, and treatment of IBS.

16.2 Definition and Subtypes of Irritable Bowel Syndrome

Since IBS is not an organic disease and does not have biological markers, it is diagnosed after testing for various organic diseases with similar symptoms and confirming that there are no organic causes. Therefore, the symptoms reported by patients constitute the most important evidence for diagnosis. After the awareness of FGIDs, including IBS, a classification system for research and clinical diagnosis became necessary. As there were no standards or research-based evidence at the time of the 1988 International Congress of Gastroenterology in Rome, they developed diagnostic criteria by con-

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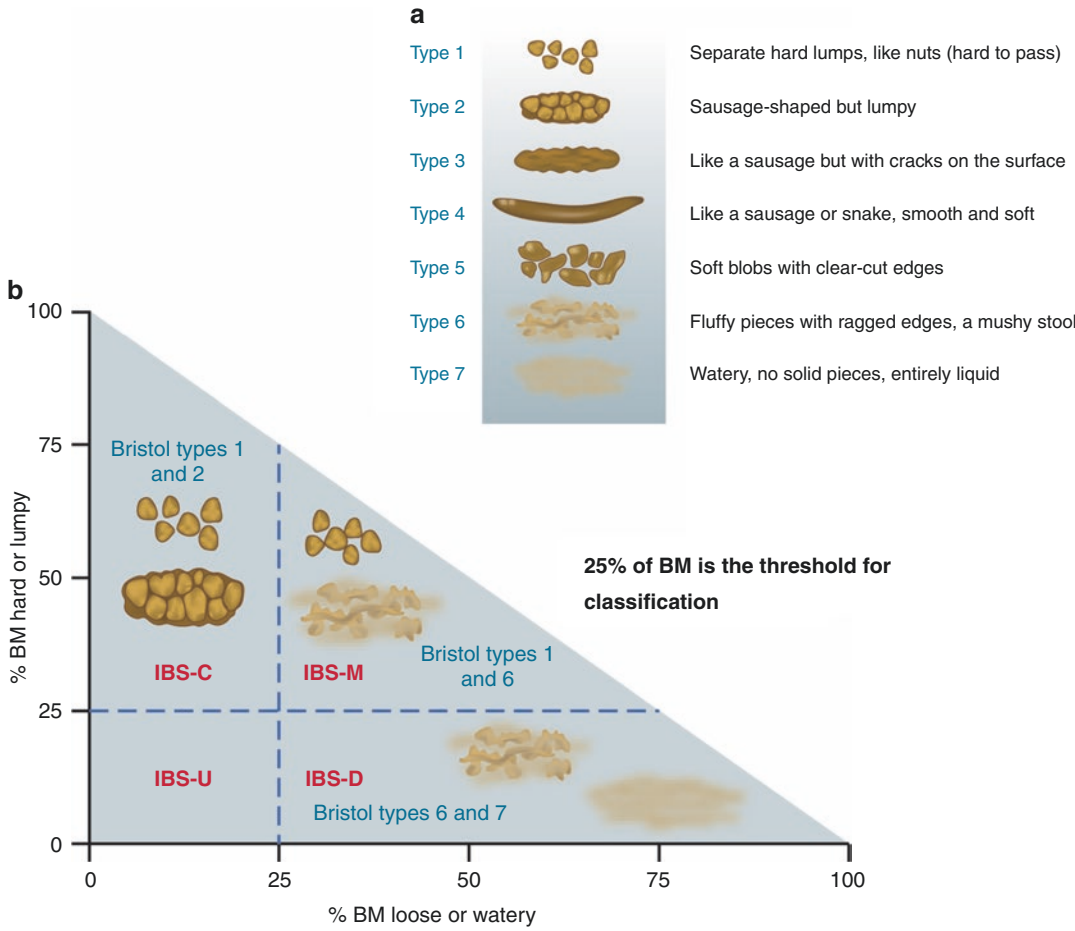

Fig. 16.1 Forms of stool, which are important for the diagnosis of IBS (**a**) and the criteria to determine the subtype of IBS (**b**). *IBS* irritable bowel syndrome (adapted from Lacy et al. [6])

sensus through the Delphi approach. However, as new data accumulated, revision of diagnostic criteria is needed for evidence-based approach. Thus, the Rome I diagnostic criteria was published in 1994, Rome II 2000, Rome III 2006, and Rome IV 2016 [6]. If research on the concept and pathophysiology of FGIDs accumulates, then the guidelines for FGIDs is expected to be updated. IBS is diagnosed if patients experience repeated abdominal pain for more than 1 day per week in the past 3 months and two or more items from the below list are present.

1. Abdominal pain is related to defecation.
2. Changes in the frequency of defecation.
3. Changes in the form of stool.

Moreover, while meeting the criteria for the past 3 months, the symptoms must have started at least 6 months ago [6]. Although not included in the criteria, symptoms that support the diagnosis are as follows: the frequency of defecation is less than or equal to three times a week or more than or equal to four times a day; the stool is thick, hard, loose, or watery; defecation needs to be forceful for expulsion; the need to defecate is urgent; defecation feels incomplete; the stool is mucous; and there is bloating. In the Rome II diagnostic criteria, IBS was categorized into IBS-C and IBS-D, but the stool can be hard even when the frequency of defecation is high (pseudodiarrhea), and on the other hand, stool can be loose or watery even when defecation is force-

ful. Usually, the form of stool reflects the duration of movement through the intestine, but symptoms such as forceful defecation, an urgent need for defecation, a sensation of incomplete defecation, and the frequency of defecation could be not related to the form of stool. Therefore, the Rome IV diagnostic criteria used the Bristol stool chart (Fig. 16.1a) to compensate these problems. That is, IBS was classified as IBS-C when types 1 and 2 account for more than 25% of bowel movements and types 6 and 7 are less than 25% and as IBS-D when types 6 and 7 account for more than 25% of bowel movements and types 1 and 2 are less than 25% (Fig. 16.1b). Based on these forms of stool, four subtypes—IBS-C, IBS-D, IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U)—were proposed [6] (Fig. 16.1b).

16.3 Epidemiology and Prevalence of Irritable Bowel Syndrome

The prevalence of IBS is known to be 10–20% internationally, but it was lower in South Korea, at around 2.2–6.6% based on Rome criteria. Its prevalence among women is about 2–2.5 times higher than its prevalence among men in all circumstances, and this finding is consistent across studies [8, 9]. However, there have been reports that this sex/gender difference was not observed in some parts of Asia and South America. According to a systematic review conducted by the Rome Foundation Committee with 83 studies in 41 countries including 288,103 individuals (55% women), the prevalence was 10.2% among women, which was higher than the prevalence of 8.8% among men, and this same phenomenon was also observed in Asia and South America [10]. In another meta-analysis with 55 studies including 162,543 individuals, the prevalence was significantly higher in women than in men (14.0% among women and 8.9% among men; odds ratio [OR] 1.67; 95% confidence interval [CI], 1.53–1.82) [11]. However, this sex/gender difference varied by region (Cochran Q, 82.89; $p < 0.001$) [12], and this variation can be attributed to the hygiene hypothesis and differences in the gut microbiome, diet, and utilization of hospitals [13].

The frequency of IBS does not demonstrate sex/gender differences until puberty, but differences can be observed subsequently [14]. In women, IBS frequently occurs in the late teens, increases until mid-40s, and decreases afterward until it becomes similar to that of men in the 70s [14], which suggests the influence of sex hormone. In contrast, in men, it increases from 20s but remains relatively stable until the 70s [14, 15]. Further evidence for this possibility is drawn from observations that IBS is affected by menstruation, pregnancy, menopause, and hormone replacement therapy [14, 16].

16.4 Symptoms of Irritable Bowel Syndrome

IBS is categorized into four subtypes (Fig. 16.1b)—IBS-C, IBS-D, IBS-M, and IBS-U—based on the Bristol stool types [6] (Fig. 16.1a). However, since the form of stool is not completely consistent, the categorization is based on a threshold of 25%. In addition, based on whether abdominal pain is experienced, functional constipation and IBS-C are differentiated. Similarly, IBS-D and functional diarrhea, which is diagnosed when there is repeated diarrhea without pain, are differentiated, and these two conditions can change into each other [6] (Fig. 16.2). There are substantial sex/gender differences in types, as IBS-C is more common among women and IBS-D is more common among men [11, 12, 17–19]. In a meta-analysis of 22 studies, women reported symptoms related to pain and constipation more frequently than men (all $p < 0.05$), and men reported symptoms related to diarrhea more often [19]. The pooled prevalence of IBS-C among women was 40%, while it was 21% among men (OR 2.38; 95% CI, 1.45–3.92), and the pooled prevalence of IBS-D among women was 31%, while it was 50% among men (OR 0.45; 95% CI, 0.32–0.65) [19]. There were no observed differences in the

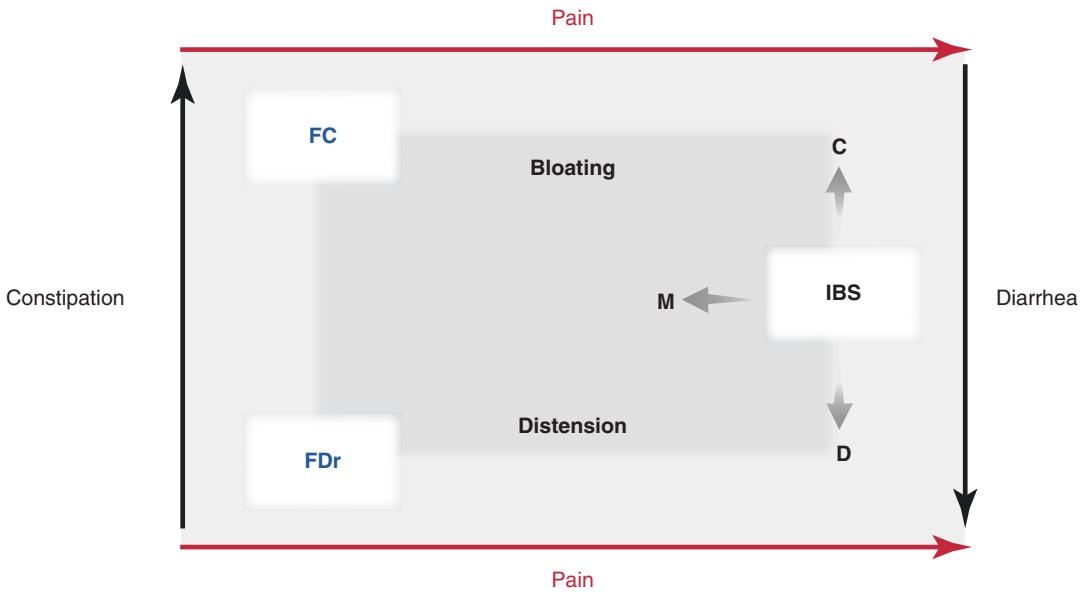

Fig. 16.2 IBS subtypes and their relationships with functional constipation and functional diarrhea. *IBS* irritable bowel syndrome (adapted from Lacy et al. [6])

pooled prevalence of IBS-M (25.8% among women and 25.0% among men) (OR 1.07; 95% CI, 0.84–1.38) [19], indicating that the large sex/gender differences are due to IBS-C in females and IBS-D in males. Chronic pain disorders such as fibromyalgia, chronic fatigue syndrome, and migraines are common in female IBS patients, suggesting a connection to hormones [14, 16, 20–23]. This hypothesis is supported by IBS symptoms such as loose stool, bloating, and exacerbated abdominal pain reported during menstruation [14]. Similarly, a study of community members in Iceland observed that IBS symptoms were more severe in females who experienced dysmenorrhea than those in females who did not experience dysmenorrhea, and a study that used an ovulation kit found that IBS was exacerbated in the late luteal phase and in the beginning of menstruation when estrogen and progesterone levels are low [24]. IBS symptoms are clearly different between males and females, whose sex hormones differ, but the results regarding IBS in females according to menstruation cycle or pre- and post-menopausal status are rather inconsistent, suggesting the need for more studies.

Sex/gender differences in IBS symptoms relate to quality of life (QoL), resulting in major differences in the QoL of women and men with IBS. Female patients with IBS had low QoL, high levels of stress, depression, anxiety, and low self-control [25], and bloating, flatulence, and rumbling in the abdomen were more common among women. Dissatisfaction with defecation and health anxiety were also higher among women [26]. A study conducted in South Korea found significantly lower health-related QoL among women than among males, and QoL was lower in the women with a relatively low education level [27]. The low QoL among patients with IBS has been explained by psychological factors [28–30].

16.5 Pathophysiology of Irritable Bowel Syndrome

It is hypothesized that genetic factors, changes in intestinal motility, visceral hypersensitivity, psychosocial factors, imbalances in neurotransmitters, infection, and inflammation influence the pathogenesis of IBS. However, its pathophysiology is not completely understood, and interrelated mechanisms are thought to cause IBS. The current understanding is that disorders in the brain-gut axis, which is composed of the interactions among the intestinal tract, the enteric nervous system, and the central nervous system, cause changes in intestinal motility, visceral hypersensitivity, and disorders in the autonomic nervous system. In addition, environmental factors such as various psychosocial factors, infections, and inflammation responses impact this process. The effect of hormones is interpreted as causing the higher prevalence among females and more severe symptoms, while the tendency to be more vulnerable to stress in sociocultural relationships is thought to lower the QoL among women with IBS. In this review, the pathophysiology of IBS is summarized with a focus on sex/gender-specific medicine.

16.5.1 Hormonal Factors

The changes in intestinal motility, visceral hypersensitivity, and disorders in the autonomic nervous system observed in patients with IBS are known to be caused by the brain-gut axis. Female sex hormones are related to the nervous system and emotional system and influence stress and sensitivity toward intestinal motility and visceral pain [26]. Estrogen and progesterone suppress smooth muscle contraction, and progesterone affects the 5-hydroxytryptamine (5-HT) system, which controls peristaltic movement of the large intestine. However, there was a report that female patients with IBS experience constipation at times when they are not menstruating and when they have low blood levels of ovarian hormones [31]. In general, the gastrointestinal transit time is longer in females than in males [32], and the transit time is longer when the levels of female ovarian hormones are high, indicating a close association between sex hormones and intestinal contraction [33]. The role of male sex hormones is being discovered as well. Androgens suppressed chronic pain syndrome and had analgesic effects in an experimental pain model [34]. It is hypothesized that androgen levels, receptors, and area of activity have a role in the incidence of IBS and chronic pain syndrome [35]. According to a recent study, middle-aged males with IBS had lower luteinizing hormone levels than healthy males, and it was reported that IBS symptoms were inversely proportional to testosterone [36]. Sex hormone-binding globulin (SHBG) and testosterone were elevated in young male patients with IBS [36], suggesting that male sex hormones play a role in the occurrence of IBS, but more studies are necessary, as this finding is contrary to what has been reported in the past.

16.5.2 Changes in Intestinal Motility

Motility abnormalities have been observed in 25–75% of patients with IBS. Increases in intestinal motility due to various stimuli such as food, balloon distension of the colon, stress, and cholecystokinin (CCK) are more drastic in IBS patients than in healthy individuals. High-amplitude propagating contractions (HAPCs), which are related to abdominal pain, are significantly increased in patients whose main symptoms are diarrhea and abdominal pain. In contrast, high-amplitude contractions in the intestines are decreased in IBS-C patients, and the total intestinal transit time is long. Intestinal motility abnormalities cause symptoms in relation to the lower sensitivity threshold than that of healthy controls. Regarding such intestinal motility abnormalities, IBS-C, in which intestinal motility slows down, is more common among women, and IBS-D, in which intestinal motility is more active, is more common among men. In addition, abdominal pain is more severe among women, which is difficult to understand at first glance. Abdominal pain is not the direct result of intestinal motility—instead, it is a phenomenon caused by

visceral hypersensitivity—so an interpretation from multiple perspectives is necessary.

16.5.3 Visceral Hypersensitivity and Brain-Gut Interactions

Research on visceral hypersensitivity and brain-gut interactions suggests that many symptoms of IBS are caused by exaggerated perceptions of visceral stimuli that occur in the gastrointestinal tract, as 50–70% of IBS patients experience discomfort when the intestines are expanded and demonstrate a low pain threshold. Visceral hypersensitivity in patients with IBS can be observed both in the large intestine and in the small intestine. In healthy controls, pain from balloon distension is experienced in only one location, but patients with IBS experience pain in multiple locations and radiating pain. Internal sensory information is delivered to the central nervous system through the afferent neural pathways known as the brain-gut axis. When there are abnormalities in the upregulation process of afferent signals in one or more locations, visceral hypersensitivity and abdominal pain and discomfort are experienced. Visceral hypersensitivity causes symptoms by increasing the efferent stimulation to the intestinal tract and inducing changes in intestinal motility through the amplification of the afferent-efferent reflex of the intestinal tract. As the concept of the visceral nervous system has been established and many studies about the interactions between the central nervous system-gastrointestinal tract have been conducted, it has become clear that the changes in intestinal motility, visceral hypersensitivity, and disorders in the autonomic nervous system observed in IBS are controlled by the brain-gut axis. The importance of the gut microbiome has recently been emphasized, and the concept was expanded to the brain-gut-gut microbiome axis. The motor and sensory pathways of the visceral nervous system are connected to the central nervous system through the sympathetic and parasympathetic nervous systems. When various substances such as serotonin, bradykinin, adenosine, prostaglandins, and proteases accumulate due to inflammation in the intestinal tract, ischemia, or psychological factors such as stress, the sensitivity toward the stimulation of sensory afferent fibers located in the intestines increases. There are also reports that even though nerve stimulation delivered to the central nervous system is normal, there are disorders in the process of the stimulation being interpreted in the brain. In this process, gender influences the threshold for visceral pain in both healthy individuals and patients with IBS [9], and women experience more severe, frequent, and lasting pain [37, 38]. At the same time, women have a lower pain threshold when the intestines are expanded than men, reporting more frequent pain and stomach discomfort [17, 33, 39–41]. Female patients with IBS are known to have similar or lower pain thresholds compared to healthy female controls [37, 39]. The most important cause of this phenomenon is hormones. Estrogen is a central nervous system stimulant, while androgen receptors suppress the central nervous system [42] (Fig. 16.3), reducing chronic pain syndrome [38]. At the same time, compared to male patients with IBS, female patients with IBS demonstrate structural and functional differences in the brain such as higher activation in the areas that process emotion such as the amygdala and infragenual cerebral cortex in response to intestinal stimuli [33].

16.5.4 Infection, Inflammation Response, Immune Response, and Postinfectious Irritable Bowel Syndrome

IBS is associated with low-grade inflammation, and changes in cytokine levels have been observed in IBS. A meta-analysis also found sex/gender differences [43, 44]. That is, serum tumor necrosis factor-α (TNF-α) levels were higher among female patients with IBS than among male patients with IBS, and interleukin (IL)-10 was lower among male patients with IBS than among healthy controls, suggesting that IL-10 is a protective factor against IBS [45]. Sex/gender-specific studies on inflammatory cytokines and IBS showed that IL-17 and TNF-α levels were high in

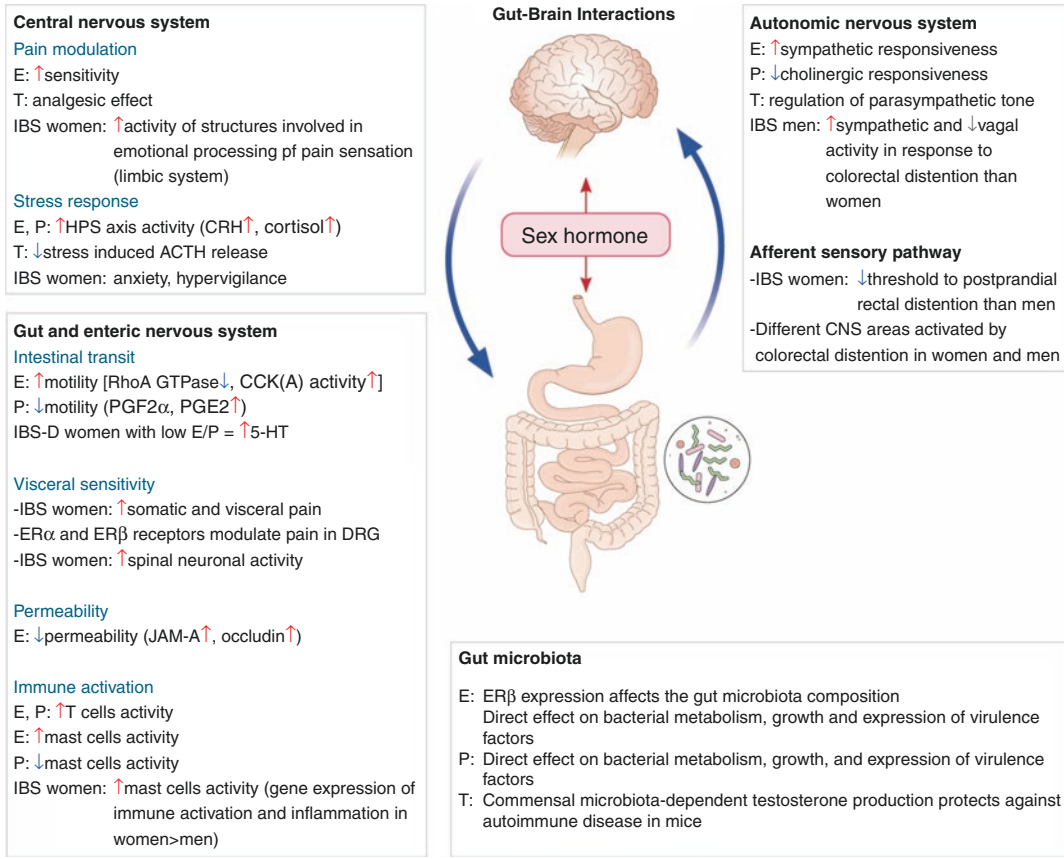

Fig. 16.3 The effect of sex hormones in the pathophysiology of IBS. *IBS* irritable bowel syndrome (adapted from Kim and Kim [42])

females and IL-10 levels were lower in females and males [26]. Compared to males, female patients with IBS had greater mast cell infiltration in the intestines and decreased levels of CD3+ and CD8+ T lymphocytes [45], indicating sex/gender differences in the immune mechanism of IBS. The author also measured intestinal inflammatory factors and factors related to intestinal permeability among patients with IBS, and the results indicated that both female and male patients with IBS-C had significantly increased levels of transient receptor potential vanilloid-1 (TRPV1), nerve growth factor (NGF), and glial cell-derived neurotrophic factor (GDNF) (all $p < 0.05$) [40]. Serum IL-1β levels significantly increased among female patients with IBS-C ($p < 0.002$), indicating that such neurotrophic factors and IL-1β contribute to IBS-C [46]. However, these factors did not demonstrate significant changes in IBS-D, and instead, female patients with IBS-D had decreased levels of zonula occludens-1 (ZO-1), a tight junction protein, suggesting different mechanisms depending on the subtype of IBS and sex/gender differences [46].

IBS that occurs rapidly after acute infection accounts for around 6–17% of all IBS cases, and approximately 7–31% of patients who completed treatment for acute infections had IBS. Mast cell infiltration in the myenteric plexus and muscle layer of the intestines is observed among such patients, the number of enterochromaffin cells increases in the intestinal mucosa, and lymphocyte infiltration into the intestinal plexus is prominent. Symptoms similar to IBS are observed in a high percentage of patients with inflammatory bowel diseases, especially in the post-remission

state of ulcerative colitis. Sensory-motor changes in the intestines which occur in the acute deteriorated stage of inflammatory bowel diseases are maintained even after remission occurs, causing symptoms of IBS. The risk factors of postinfectious IBS are age 60 and below, female sex, more than 7 days of acute infection, no vomiting, psychological factors such as hypochondriasis or a history of stress before infection, and pathogen-related factors. Female sex showed an OR of 2.19 (95% CI, 1.57–3.07) [47], and it is reported that IBS occurs more frequently when the enteritis is severe. Postinfectious IBS patients have shorter intestinal transit time and increased visceral sensations and local reflexes, demonstrate malabsorption of bile acids, and have increased enterochromaffin cells that contain serotonin in the intestines. These suggest that inflammation and immune activation are the main pathophysiological components of postinfectious IBS. It starts as acute inflammation in patients with a genetic pre-disposition. The low-grade chronic inflammation maintained by increased exposure to intestinal antigens due to the increased permeability of the intestinal mucosal epithelium is the main pathophysiology of postinfectious IBS. If there is a clear history of acute symptoms and two conditions out of fever, vomiting, diarrhea, and positive fecal culture test are met, postinfectious IBS can be diagnosed. If there is continuing weight loss or bloody stool, other diseases must be considered.

16.5.5 Intestinal Permeability

Psychological stress is known to increase the cell permeability of the intestines through the activation of mast cells and eosinophils [48–51], and females had severely and constantly impaired absorption of albumin, mannitol, and xylose when cold pain stress was introduced to the jejunal lumen [52]. In addition, chronic psychological stress reduced the expression of epithelial tight junction proteins such as claudin-1, occludin (OCLN), and ZO-1 through the mediation of corticosterone which increased intestinal permeability [52]. Interestingly, estrogen was found to play a role in this process [52]. Estrogen aided the penetration of calcium and vitamin D in Caco-2, a colorectal cancer cell line [53], and increased the expression of mRNA and proteins of OCLN and junction adhesion molecule A in the intestines of female mice [54]. Estrogen receptors were activated in female mice who had phytoestrogen-rich soy germ-fermented ingredients orally injected for 2 weeks, suppressing intestinal permeability and intestinal hypersensitivity caused by stress [55]. According to an experiment on intestinal inflammatory factors and factors related to intestinal permeability among patients with IBS, inflammatory factors and factors related to intestinal permeability were significantly higher in the IBS-C group than in the control group (all $p < 0.05$), and *ZO-1* mRNA expression was significantly lower among female patients with IBS-D than among controls ($p = 0.021$) [46], indicating that an increase in intestinal permeability can explain IBS-D and that estrogen plays a role in this process. However, more detailed studies are needed.

16.5.6 Changes in the Gut Microbiota

Gut microbiota can be categorized largely into the microbiota in the intestinal lumen (microbiota detected in stool) and the microbiota adhering to the intestinal mucosa. The intestinal bacteria that mostly comprise gut microbiota are important in maintaining intestinal homeostasis through metabolic processes and can cause bloating or flatulence symptoms in patients with IBS through fermenting carbohydrates and producing gas. Bacteria adhering to the intestinal mucosa are present at a lower quantity, but can cause symptoms such as immune activation through interaction with the immune system of the intestinal mucosa. The gut microbiota is thus important for the normal physiology and immune management of the intestines. Disorders in intestinal motility, immune activation, and abnormal fermentation due to over-proliferated gut microbiota are thought to contribute to the pathogenesis of IBS. There are differences in the bacterial composition in stool between patients with IBS and healthy controls, especially in the composition of bacteria, the *Firmicutes* phylum. When the author

conducted 16S rRNA metagenomic sequencing of feces from 7 patients with IBS-D and 12 healthy controls and a phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt), *Acidaminococcaceae*, *Sutterellaceae*, and *Desulfovibrionaceae* were present at higher levels in patients with IBS, but *Enterococcaceae*, *Leuconostocaceae*, *Clostridiaceae*, *Peptostreptococcaceae*, and *Lachnospiraceae* were found at significantly lower levels [56] (Fig. 16.4a–i). In particular, K07007 (baiN, 3-dehydro-bile acid delta 4,6-reductase) and K15874 (baiI, bile acid 7 beta-dehydratase), which are involved in secondary bile acid production (pathway ko00121) that influences bile reabsorption, were present at significantly lower levels in patients with IBS than in controls [56] (Fig. 16.4j–k), indicating the influence of gut microbiota on the occurrence of IBS-D [56]. However, the sample size was too small, to conduct a sex/gender-specific analysis. Recently, the expression "brain-

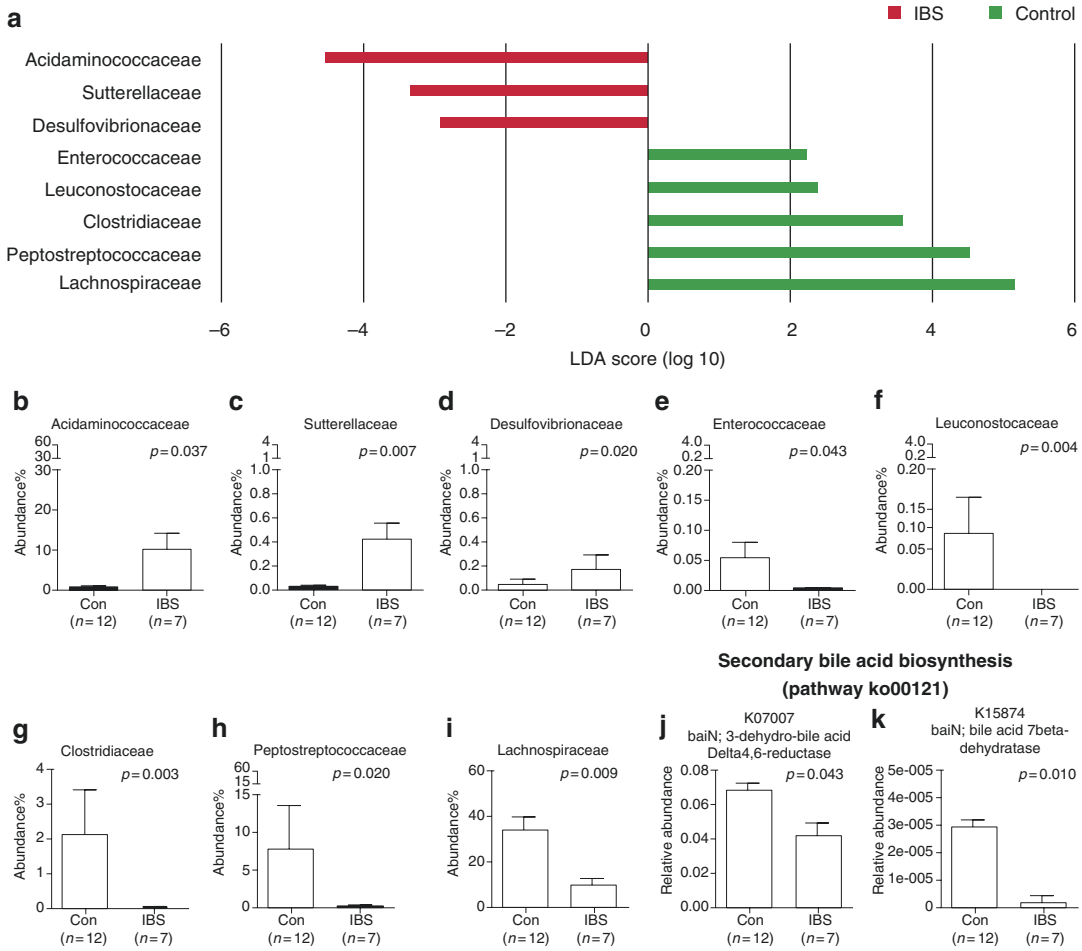

Fig. 16.4 Comparison of the gut microbiota in patients with IBS and controls. (**b**) *Acidaminococcaceae*, (**c**) *Sutterellaceae*, and (**d**) *Desulfovibrionaceae*, which demonstrate significant differences in the abundance ratio between patients with IBS and controls in a linear discriminant analysis of effect size (LEfSe) at the family level of the gut microbiota, showing significantly higher levels in patients with IBS than in controls (**a**). (**e**) *Enterococcaceae*, (**f**) *Leuconostocaceae*, (**g**) *Clostridiaceae*, (**h**) *Peptostreptococcaceae*, (**i**) *Lachnospiraceae*. (**j–k**) Among orthologues that are involved in secondary bile acid production (pathway ko00121), (**j**) K07007 (baiN, 3-dehydro-bile acid delta 4,6-reductase) and (**k**) K15874 (baiI, bile acid 7 beta-dehydratase) were significantly lower in patients with IBS than in the control group. *IBS* irritable bowel syndrome (adapted from Lee et al. [56])

gut-microbiome axis" is being used, as many evidences were accumulated regarding the importance of the gut microbiota for the brain-gut axis and barriers [42, 57, 58] (Fig. 16.3). Actually, sustained reduction in the gut microbiota and brain-gut axis imbalance cause low-grade inflammation and immune mechanism imbalance, leading to intestinal secretions, visceral pain, and changes in intestinal motility [48]. Sex hormones influence bacterial metabolism and influence the expression of bacterial virulence factors through the expression of nuclear steroid receptors such as estrogen receptor β (ERβ) [59]. Exposure to microbiota in infancy impacts the level of sex hormones, changing the progression of autoimmune diseases in insulin-dependent diabetic mice models [60]. In a similar context, when testosterone secretion increased in pubescent male mice models, changes in the gut microbiota and T and B lymphocytes, which are related to autoimmune diseases, occurred [60].

There are several evidences that small intestinal bacterial overgrowth (SIBO) can be important in IBS. Normally, the stomach has a relatively small number of bacteria due to peristalsis and a low pH from gastric acid. There are 0–1 × 10^3 colony-forming units (CFU)/mL per 1 mL of stomach content, while there are 1–1 × 10^4 CFU/mL in the duodenum and jejunum, 1–1 × 10^5 CFU/mL in the proximal ileum, 1 × 10^5–1 × 10^8 CFU/mL in the terminal ileum, and 1 × 10^{10}–1 × 10^{12} CFU/mL in the colon. *Lactobacillus* spp., *Enterococcus* spp., and *Streptococcus* spp., as benign aerobic bacteria that are a part of the oral flora, and facultative anaerobes exist in the small intestines, while facultative anaerobes such as *Bacteroides* spp., *Clostridium* spp., *Bifidobacterium* spp., *Fusobacterium* spp., and *Eubacterium* spp. make up around 99.9% of the microbiota in the large intestine. Overproliferation of bacteria in the small intestine refers to bacteria in the intestines or the distal small intestine expanding into and inhabiting the proximal small intestines and is defined by bacteria in the proximal small intestines proliferating to more than 1 × 10^5 CFU/mL. The prevalence of SIBO (>10^3 coliforms per mL) in patients with IBS-D was 60% compared with 27.3% of IBS patients without diarrhea (p = 0.004) [61] Since IBS-D, bloating, and abdominal pain are more common among females, it can be hypothesized that SIBO is also more common among females. However, sex/gender differences have not been reported, yet, in this regard, and further research is needed.

16.5.7 Psychosocial Factors

Patients with IBS are more likely than healthy controls to have experienced severe stress such as abuse during childhood. Such stress is closely related to the onset and severity of IBS symptoms, and in 40–90% of patients with IBS, psychiatric disorders co-occur. Psychological and psychosocial factors affect disease progression and treatment results of patients with IBS, and psychosocial stressors cause symptoms through the amplification of central nervous system signaling regarding changes in intestinal functions and normal intestinal signals. Changes in intestinal physiology and psychosocial factors are combined through the brain-gut axis to influence the symptoms, disease behavior, and ultimately disease progression and prognosis. Sex/gender differences cause IBS symptoms depending on individuals' sense of responsibility and social roles (e.g., unpaid childcare and work, which are stressful) and also influence healthcare-seeking behaviors [62–64]. When IBS symptoms are present, society has certain expectations about how individuals will react according to their sex/gender, and these expectations affect healthcare-seeking behaviors; therefore, behaviors in response to symptoms among patients with IBS can differ by sex/gender [62]. Women believe that bodily phenomena are more private than men do, feel that a loss of control is very shameful, and believe they should be thin and attractive [63]. Women also worry more than men about the effects of IBS, such as their abdomen appearing bigger due to bloating, having to go to the bathroom more often due to diarrhea, and having a foul odor [13]. Women worry a lot about not being able to function in their roles as wives,

mothers, and workers due to IBS symptoms, while men are more threatened by the fact that they have IBS, which is more common among women, that they feel weak, and that they cannot perform the duties necessary to be responsible for their family [65]. Along with the pathophysiology of IBS, doctors should understand the sex/gender differences in the responses toward IBS symptoms to help with treatment [65].

16.5.8 Dietary Factors

Many patients with IBS believe that food sensitivity contributes to the pathophysiology of IBS since their symptoms are triggered or exacerbated by ingesting certain foods. Lactose intolerance, fructose intolerance, and food allergies have been hypothesized as mechanisms, but this did not fully explain the association with IBS symptoms. It was recently found that fermentable mono-, di-, and oligosaccharides and polyols, which are not easily absorbed and are easily fermented in the intestines, are associated with IBS symptoms. The main examples are fructan, raffinose, lactose, polyol, and galactan, which are referred to as FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols). Galactan is mostly found in onions, cabbage, and beans, and fructan is abundant in wheat, onions, spring onions, chives, and chicory. When these items are consumed excessively, bloating and diarrhea similar to IBS symptoms occur through the maintenance of high osmotic pressure in the small and large intestines, which indicates that FODMAPs can be a cause of IBS. Since food preferences differ by sex/gender and preferences also shift with age, the distribution of gut microbiota that decompose food is different by sex/gender. Therefore, FODMAPs must contribute to the experience of IBS symptoms in some manner. As it is clearly distinguished whether Western food, such as food consumed in Australia, contains FODMAPs, apps have been developed accordingly. However, no studies have examined sex/gender differences in the consumption of FODMAPs, so far.

16.6 Treatment of Irritable Bowel Syndrome

IBS is not a life-threatening disease, but it lowers the QoL and productivity by requiring frequent visits to doctor's offices. Therefore, active treatment is needed. Appropriate disease history-taking and examination are important, and mutual cooperation with the patient is essential [42]. An explanation of the progress of the disease and reassurance are the most important aspects of the clinical encounter, and beyond that, psychological stress relief, diet, changes in gut microbiota, and drug therapy are used as treatment. Some patients with IBS do not respond to these active treatments. In a multi-center study in Japan, risk factors for non-response were low mental component summary (MCS) score and female sex [66]. Treatment results were not favorable in women because the factors that decrease the effectiveness of IBS treatment, such as depression, anxiety, and intense psychological symptoms [67, 68], are observed more frequently in women. IBS occurs more commonly in women, who are sensitive to stress, and the pathophysiology of IBS is influenced by sex/gender differences; therefore, sex/gender-tailored medicine is very important for treating IBS appropriately.

16.6.1 Overall Drug Treatment

Drug treatment for IBS is not necessary for all patients, and patients whose QoL is reduced due to symptoms are the treatment target. However, the placebo effect is high (20–50%), suggesting the importance of explanations about the disease progress and reassurance. The treatment of IBS aims at the alleviation of overall symptoms such as abdominal discomfort, bloating, and changes in defecation habits, so medications effective for each main symptom such as abdominal pain, diarrhea, and constipation are used. An overall principle is that anticonvulsants such as anticholinergics, calcium channel blockers, and opioid receptor modulators relax or inhibit contraction of the intestinal smooth muscle. Bulk-forming

laxatives are effective for the treatment of diarrhea and can increase the frequency of bowel movements, but they can also exacerbate bloating or stomach discomfort in some patients, requiring caution. Loperamide, an antidiarrheal, is very effective in treating diarrhea, decreasing the frequency of bowel movements, and improving the form of stool, but it is not effective for the overall IBS symptoms, abdominal discomfort, and bloating. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) improve abdominal pain in patients with IBS but do not improve overall symptoms or other types of symptoms. Especially since the most common and dose-responsive side effect of TCA is constipation, the use of TCAs in patients with IBS-C should be considered with caution. In summary, when abdominal pain is the main symptom, antipsychotic agents and TCAs are used. When diarrhea is the main symptom, antidiarrheals, antipsychotic agents, and cholestyramine are used. In the case of IBS-C, laxatives and a high-fiber diet are used. When patients report intestinal gas, simethicone, pancreatic enzymes, and prevention of swallowing air are recommended. It is known that there are sex/gender differences in the response to such treatments [69], but sex/gender differences in loperamide, atropine, diphenoxylate, and cholestyramine, which are widely used, are unknown [19, 70, 71]. An explanation may be that most clinical studies were conducted among women [72], but serotonin 5-HT_3 receptor antagonists are drugs for which sex/gender differences were found in a recently conducted clinical study. 5-HT_3 receptors exist in the limbic system and cortical region of the central nervous system, as well as the emetic center, and are located in the post-synaptic enteric nervous system in the afferent sensory nerves, the myoclonic plexus, and the submucosal plexus. 5-HT_3 antagonists are used as drugs for IBS-D, as 5-HT_3 receptors are involved in visceral pain, intestinal transit time, and gastrointestinal secretion. The effectiveness of ramosetron and alosetron, which are 5-HT_3 antagonists, and 5-HT_4 agonists is greater in females than in males, but the mechanism has yet to be understood [73–76]. In a recent clinical trial of alosetron, a 5-HT_3 antagonist, with only males, abdominal pain, abdominal discomfort, and stool improved, but other IBS symptoms did not, supporting its greater effectiveness among females [77]. However, a meta-analysis of randomized controlled trials reported that it was effective for both males and females [78, 79]. Tegaserod, a famous 5-HT_4 agonist, is also known to be effective in females [71, 80], but since the number of males who participated in the clinical trial was too small, it is difficult to discuss sex/gender differences regarding this drug.

Based on the observation that there are family trends in IBS, it has been hypothesized that there are genetic factors beyond the common environmental factors. Serotonin transporter-linked polymorphic region [5-HTTLPR], a 44-bp insertion/deletion of *SLC6A4* (serotonin reuptake transporter) (a neurotransmitter), creates short (S) and long (L) alleles that have different transcriptional efficiencies, suggesting an association with IBS [81]. The author recently reported that the L/L genotype was associated with overall IBS, IBS-C, and IBS-M [81] and serum serotonin levels were lower in patients with IBS-C than patients with IBS-D or controls [82]. It was also indicated that the sex/gender differences in the 5-HT signaling system are related to the differences in the effectiveness of 5-HT_3 antagonists [83]. For example, expression of *SLC6A4* mRNA was higher in the rectal mucosa of female patients with IBS-D than in that of males [83].

16.6.2 New Drug Therapies

Excretion of the intestinal chlorine ion (Cl^-) is essential to control the movement of intestinal bodily fluids and electrolytes. Cl^- enters the cell through the Na^+-K^+-Cl^- cotransporter located in the basolateral aspect of the cell and accumulates in the cell. When the electrochemical equilibrium is exceeded, Cl^- is excreted out of the cell through the apical Cl^- channel, along with bodily fluids. There are three known channels through which Cl^- is secreted to the intestines, which are cystic fibrosis transmembrane conductance regulator (CFTR), calcium-activated chloride channel

(CaCC), and type-2 chloride channel (ClC-2). Most of the movement of Cl^- through the apical cell membrane occurs through the cyclic adenosine monophosphate-dependent CFTR (cAMP-dependent CFTR) Cl^- channel. Lubiprostone is a bicyclic fatty acid ($C_{20}H_{32}F_2O_5$) derived from metabolic products of prostaglandin E1 and ClC-2 activator, which activates ClC-2 in the apical cell membrane of the intestinal epithelium, increases the intra-intestinal movement of Cl^-, and increases the secretion of intra-intestinal bodily fluid. Two clinical trials were conducted to examine the effectiveness for IBS-C, in which 8 μg of lubiprostone or placebo was given to 1154 patients with IBS-C diagnosed using the Rome II diagnostic criteria (92% female) two times a day. IBS symptoms (abdominal discomfort, pain, defecation habits, etc.) improved in the lubiprostone group compared to the placebo group (study 1, 13.8% vs. 7.8%; study 2, 12.1% vs. 5.7%) [84]. Based on the results of those clinical trials, lubiprostone was approved in 2008 by the US FDA as a treatment for IBS-C in females of age 18 or older (8 μg, twice daily). When a clinical trial was conducted with a small sample, it was more effective for female patients with IBS-C than for males [69], but in a study with a larger sample of patients with chronic and idiopathic constipation, it was effective for both males and females, indicating that a sufficient number of males and females must be included in a study to determine sex/gender differences [85].

The next drug introduced was linaclotide, a guanylate cyclase C receptor agonist that increases cyclic guanosine monophosphate, which in turn stimulates the intra-intestinal secretion of Cl^- and carbonate ion (HCO_3^-) and suppresses the intra-intestinal Na^+ absorption by Na^+/K^+ exchangers through the CFTR Cl^- channel-dependent mechanism and a low-level CFTR Cl^- channel-independent mechanism. In a phase II clinical trial, this drug decreased intestinal transit time in a group of female patients with IBS-C who took 1000 μg of linaclotide compared to the placebo group [86] and significantly improved symptoms including abdominal pain [87]. The results from a phase III clinical trial with 805 patients with IBS-C in 2010 showed significant or complete improvement in symptoms among 39.4% of patients in the linaclotide treatment group and 16.6% of patients in the placebo group, which resulted in FDA approval. Linaclotide is known to be effective in both males and females [88, 89].

16.6.3 Drug Treatment Related to Gut Microbiota

Differences in the gut microbiota between healthy controls and patients with IBS have been established [90]. The most commonly used antibiotic in patients with IBS is rifaximin. Rifaximin is a derivative of rifamycin and has broad sensitivity toward gram-positive, gram-negative, aerobic, and anaerobic bacteria. There is little concern about systemic side effects since there is almost no systemic absorption when taken orally. It is appropriate for patients with IBS and overproliferation of bacteria in the small intestines who require repeated treatment since there have been no reports of resistant strains after long-term use. As it is also sensitive to *Clostridium difficile*, the cause of pseudomembranous colitis, there are also little concerns about antibiotic-related diarrhea and pseudomembranous colitis. When a randomized controlled trial of non-absorbed antibiotic rifaximin was conducted for 2 weeks with patients with IBS except IBS-C (TARGET 1 and TARGET 2, 67% female), IBS symptoms, bloating, abdominal pain, and loose or watery stool significantly improved [91]. A study of patients with reoccurring IBS-D (68% female) still showed the effectiveness of repeated use of rifaximin [92]. However, sex/gender differences are unknown since sex/gender-specific analyses were not conducted.

The evidence supporting the use of *Lactobacillus* formulations in patients with IBS is that *Lactobacillus* formulations lead to interference with pathogen adhesion by binding to mucosal epithelial cells, reinforcement of epithelial barrier function, changes of fermentation in the intestines, changes of mucosal response to stress, an immunomodulatory effect, reduction of visceral hypersensitivity through increased

expression of opioid and cannabinoid receptors in the intestinal epithelial cells [93], and reduction of inflammation to low levels [94]. In a recent meta-analysis with 18 randomized controlled trials, *Lactobacillus* formulations aided the treatment of IBS and were effective in 1 out of 4 patients [95]. Since the gut microbiota of males and females differ, it is hypothesized that the male-to-female ratio of study participants would impact the effect, but no data have clarified this point yet. The author's research team recently conducted a study with a model of IBS-induced Wistar mice [49]. When a low-grade inflammation was induced through the psychological anxiety created by placing mice on top of a plastic box floating on water for 1 h per day for 10 days (repeated water avoidance stress, rWAS), female Wistar rats experienced diarrhea more than male rats, experienced visceral analgesia, and had greater levels of mast cell infiltration in the distal intestines and mucosal cytokines [49]. When *Lactobacillus farciminis* (1 x 10^{11} CFU/mL once every day) was given orally, the treatment effect in terms of both symptoms and the reduction in mast cells and cytokines was significantly greater in female rats than in male rats [49]. Based on this result, the role of the gut microbiota in IBS, as well as responses to treatment, differs by sex/gender, an area that requires further clinical studies.

16.6.4 Psychiatric Treatment

The anterior cingulate cortex is less activated, while the prefrontal cortex is more activated in patients with IBS than in controls. The anterior cingulate cortex is a region of the limbic system and is related to opioid receptor activation, and the prefrontal cortex is closely related to hyperarousal and anxiety. Various types of psychiatric treatment such as cognitive behavioral therapy, interpersonal therapy, and hypnotic therapy increase the activation of the anterior cingulate cortex, which is related to opioid receptor activation, and reduce the activation in the brain areas that expand pain sensation resulting in the decrease of pain perception. Patients with IBS are more likely to have psychiatric disorders such as depression, anxiety, and affective disorders than healthy individuals. Somatization disorder is a predictive factor of FGIDs, present in at least 25% of patients with IBS who visit a tertiary hospital. Patients with IBS are around two to four times more likely to be using medication that acts on the central nervous system, such as antidepressants, anti-anxiety drugs, antipsychotics, sleeping pills, or sedatives than controls, so psychiatric treatment can be helpful. The exact mechanism of hypnotic therapy is not known, but it improves symptoms such as abdominal pain and bloating, extraintestinal symptoms, QoL, and psychological symptoms such as anxiety and depression and controls bowel movements [96]. Hypnotic therapy has been reported to be especially effective among women, but there are no reports on the sex/gender differences in patients with IBS. Cognitive behavioral therapy aims to correct patients' maladaptive beliefs about their pain and replace them with more reasonable thoughts, but its treatment effect on IBS is yet unknown.

The reasons for using antidepressants are that they change central pain perception and they are effective for (1) visceral pain by having an analgesic effect on the peripheral nerves; (2) intestinal movement and secretions through the choline, noradrenaline, and serotonin pathways; and (3) treating accompanying psychiatric disorders such as anxiety related to symptoms, depression, and somatization disorder, as well as sleep disorders, which can be a comorbidity of IBS [97]. Antidepressants can be broadly divided into TCAs and SSRIs. In a recent meta-analysis of 12 randomized controlled trials that were evaluated as high quality, antidepressants were found to be effective for treating IBS [98].

16.6.4.1 Tricyclic Antidepressants (TCAs)

TCAs are the most widely used class of antidepressants for the treatment of IBS. TCAs block the reuptake of neurotransmitters (serotonin, norepinephrine, dopamine, etc.) secreted in the presynaptic nerve endings and increase the level of synaptic neurotransmitters, causing

post-synaptic receptor hyperexcitation. Amitriptyline can reduce the activation of the prefrontal cortex due to balloon distension of the colon in patients with IBS. This effect was not observed when patients listened to comfortable music; instead, it was only observed when patients were exposed to auditory stressors, indicating that pain or symptoms exacerbated by stress are reduced through the central nervous system rather than the peripheral nervous system [99]. The mechanism of the effect of TCAs on IBS is still unclear, but improvements in the descending pain control mechanism or the anticholinergic effect have been suggested as possible mechanisms [100]. The effect can be delayed due to the drugs' characteristics, so a sufficient dose must be prescribed for at least 4 weeks [101].

16.6.4.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs selectively inhibit the reuptake of serotonin and increase the level of synaptic serotonin by interfering with serotonin transmission proteins in the presynaptic nerve endings. As it has little impact on receptors related to other neurotransmitters, they have fewer side effects and are tolerated very well compared to TCAs. SSRIs include fluoxetine, paroxetine, citalopram, escitalopram, sertraline, and fluvoxamine. The mechanism of SSRIs is not clear, but unlike TCAs, SSRIs improve related anxiety instead of controlling pain, increase overall happiness, increase the analgesic effect of other drugs such as TCA, and treat accompanying psychiatric conditions [100]. They reduce the mouth-to-cecum transit time and total intestinal transit time, increase intestinal phasic contractility, and cause HAPCs, suggesting that they exert a stimulating effect on bowel movement [102]. In a recent meta-analysis, SSRIs were evaluated to be effective for IBS, with a relative risk of continued IBS symptoms of 0.62 (95% CI, 0.45–0.87) compared to placebo [98]. SSRIs can be used more effectively for the treatment of patients with IBS-C [103]. Paroxetine is useful when the main symptom is diarrhea since it has a stronger muscarinic effect.

16.6.4.3 Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) prevent reuptake of both norepinephrine and serotonin and are regarded to be as effective as TCAs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine. Duloxetine is the only drug with a study with patients with IBS; it was found to be effective in improving pain, the severity of symptoms, QoL, and loose stool after being given to 15 patients without depressive symptoms for 12 weeks. Seven out of the 15 patients dropped out of the study due to severe constipation [104]. Studies on SNRIs related to IBS are very limited so far, and these three psychiatric drugs are expected to be more effective in females with higher depressive and anxiety symptoms, but reports on sex/gender differences are scarce.

16.6.5 Diet

Two-thirds of patients with IBS report that their symptoms are related to food [105]. Such symptoms lower the QoL and affect energy, sleep, and physical conditions, so food must be examined closely. The premise of dietary therapy is to exclude food that exacerbates symptoms. Lactose, fructose, allergenic food, and starches such as flour are not good for IBS patients. It is reported that women consume more food that triggers symptoms than men, indicating that women must pay closer attention to diet [106]. Female patients with IBS should increase their consumption of dietary fiber and fish and reduce their consumption of fatty foods, sweet foods, red meat, coffee, and alcohol. When dietary changes are suggested, women are more eager to reflect them in their diet than men. As mentioned before, monosaccharides and polyols, which are not easily absorbed but easily fermented in the intestines, are related to IBS symptoms, and a low-FODMAP diet improves the digestive system symptoms and stomach pain of IBS in the short term [107, 108]. However, no studies have examined whether IBS symptoms improve more in one sex/gender than the other through a low-FODMAP diet.

Table 16.1 Treatment outcomes of drug for irritable bowel syndrome depending on sex/gender (adapted from Kim and Kim [42])

Therapeutic target	Name	Dose	Mechanism of action	Effect of sex or gender
Loose stool (IBS-D)	Alosetron	0.5–1 mg peroral bid	5-HT_3 antagonist	Currently available to treat women with severe IBS-D Initially demonstrated a significant improvement in women but not in men [69, 73] Later, effective in both men and women [76, 77]
	Ondansetron	4–8 mg peroral every 8 h	5-HT_3 antagonist	Did not conduct separate analyses by sex [109]
	Cilansetron	2 mg peroral tid	5-HT_3 antagonist	Significant improvement in men compared to that in women [78]
	Tegaserod		5-HT_4 agonist	Greater efficacy in women [78] Withdrawn from US market due to cardiovascular side effects [75]
	Ramosetron	5 μg peroral qid 2.5 μg peroral qid	5-HT_3 antagonist	Initially limited to men with IBS-D [110, 111] Now: a half-dose is prescribed for women [112, 113]
	Bile acid (colesevelam)	1.875 g peroral bid	Decreased stool transit times	Limited data [19]
	Loperamide	4 mg peroral Then 2 mg with each Additional loose stool Maximum 16 mg/day	Binds gut wall opioid receptor Increases sphincter tone Decreased stool frequency	Limited data [114]
Hard stool (IBS-C)	Lubiprostone	8 μg peroral bid	ClC-2 activator	For IBS, approved for women ≥18 years with IBS-C [71, 115] Effective treatment of chronic idiopathic constipation in both men and women [71]
	Linaclotide	290 μg peroral qid	Guanylate cyclase C receptor agonist	Efficacious in both men and women [85]
	Eluxadoline	100 mg peroral bid	μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist	Efficacious in both men and women [89, 116] Contraindicated in patients with history of cholecystectomy
Altered gut microbiota	Rifaximin	550 mg peroral tid for 14 days	Presumed decrease in gas-producing bacteria	Did not conduct separate analyses by sex [65, 80]

Table 16.1 (continued)

Visceral hypersensitivity	Antidepressant	TCAs Amitriptyline, 10–59 mg Imipramine, 10–50 mg Doxepin, 10–59 mg Nortriptyline, 10–59 mg Desipramine, 10–200 mg SSRIs Citalopram, 10–40 mg Fluoxetine, 10–40 mg Paroxetine, 10–40 mg Escitalopram, 10–40 mg Sertraline, 25–100 mg SNRIs Duloxetine, 30–90 mg Venlafaxine, 75–225 mg	Various	Did not conduct separate analyses by sex [9, 117]
Abdominal pain	Dicyclomine	20–40 mg peroral qid	Antagonizes acetylcholine at muscarinic receptors, smooth muscle relaxer, inhibits bradykinin, reduces histamine-induced spasm	Limited data [9, 89]
	Hyoscyamine	0.125–0.25 mg peroral every 4 h when necessary		Limited data [9, 82]
	Peppermint oil capsule	0.2–0.4 mL tid	Smooth muscle relaxer; reduce gastric motility by acting on calcium channels (similar to dihydropyridine calcium antagonists)	Limited data [9, 82]
Bloating	FODMAP		Decreases fermentable gas-producing foods	Limited data [118, 119]
	Probiotics	Various	Repopulate the gut with more efficient bacteria	Limited data [120]
	Psychotherapy			Did not conduct separate analyses by sex [9, 79, 117]

IBS-D IBS with predominant diarrhea, *IBS-C* IBS with predominant constipation, *5-HT$_3$* 5-hydroxytryptamine 3 receptor, *ClC-2* chloride channel-2, *TCAs* tricyclic antidepressants, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitors, *FODMAP* fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, bid twice a day, tid three times a day, qid four times a day

16.7 Conclusions

It is unanimously recognized that IBS occurs more commonly in women than in men. The effect of hormones is expected to underlie this difference, but the exact mechanism has yet to be understood. Female patients with IBS report constipation, nausea, and bloating more frequently, while male patients with IBS report diarrhea more frequently. Female patients have a lower QoL than male patients and demonstrate more extraintestinal symptoms and psychological symptoms such as depression, anxiety, and somatization disorders. The changes in intestinal motility, visceral hypersensitivity, and autonomic nervous system disorders observed in IBS are known to be controlled by the brain-gut axis. Female sex hormones are associated with the neuromodulation and emotion systems and affect sensitivity to stress, bowel movement, and visceral pain. As a result, females have IBS more commonly and have more severe symptoms. Their tendency to be more vulnerable to stress lowers their QoL. More women have IBS that does not respond to treatment which is shown in Table 16.1 regarding treatment outcomes of drug for irritable bowel syndrome depending on sex/gender [9, 19, 65, 69, 71, 73, 75–78, 80, 82, 85, 89, 109–120]. An explanation for why treatment results are worse in women is that factors that reduce the treatment effect, such as depression, anxiety, and intense psychological symptoms, are more common among women, suggesting the necessity for tailored treatment.

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Functional Constipation

17

Jeong Eun Shin

17.1 Introduction

Constipation is a common functional gastrointestinal disorder (FGID) that reduces the quality of life in many patients [1]. Functional constipation (FC) is characterized by hard stools, excessive straining, the feeling of incomplete evacuation, the sensation of anorectal blockage, the use of manual maneuvers during defecation, and fewer than three bowel movements a week without organic abnormalities. These symptoms persist chronically, limiting social life and lowering the quality of life, resulting in social and economic burdens. Constipation may occur secondary to various causative diseases such as endocrine diseases, metabolic diseases, neurological diseases, mental diseases, and gastrointestinal obstruction, and therapeutic drugs are taken to control them. FC is diagnosed when there is no such cause. According to the new Rome IV diagnostic criteria, FGIDs exist on a spectrum with interrelated pathophysiological characteristics that vary according to the quantitative distribution, intensity, and severity of the patient's symptoms [2–4]. Irritable bowel syndrome with predominant constipation (IBS-C) and FC can have overlapping clinical features, and each disease is diagnosed according to the accompanying pain level. The subtypes of IBS were also suggested to have overlapping features due to changes in bowel habits [2–4]. For this reason, the clinical features, pathophysiology, and treatment of FC and IBS-C cannot be clearly distinguished. However, this manuscript deals only with FC. The main mechanisms of FC are sensorimotor disorders of the large intestine and pelvic floor dysfunction, and there are various causes such as decreased caloric intake, changes in the microbiome, and anatomical structure abnormalities. These mechanisms work in combination.

The differences in pathophysiology and clinical features between men and women are very important for understanding constipation patients and applying a diagnosis and treatment process tailored to each individual with FC in clinical practice. The purpose of this manuscript was to investigate the differences between men and women in the epidemiology, pathophysiology, clinical features, and therapeutic approaches to FC.

17.2 Definition and Classification

The diagnostic criteria for FGIDs were revised according to the Rome IV diagnostic criteria in 2016 [2, 5]. FC is a functional bowel disorder in which symptoms of difficult, infrequent, or incomplete defecation predominate. Patients with FC should not meet IBS criteria, although abdominal pain and bloating may be present but

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are not the predominant symptoms [2]. The diagnostic criteria for FC in the Rome IV criteria are shown in Table 17.1, and secondary constipation should be excluded [2]. FC includes at least two of the six symptoms shown in Table 17.1, and these symptoms should begin at least 6 months before diagnosis and present during the last 3 months.

FC is divided into normal transit constipation, slow transit constipation (STC), and functional defecation disorder (FDD) according to colonic transit time and anorectal function, but they are expressed in overlapping forms rather than being distinct from each other. FDD is characterized by paradoxical contractions or inappropriate relaxation of the pelvic muscles during defecation attempts or inadequate propulsion [6]. Although patients with FDD may experience excessive straining and the sensation of incomplete evacuation or require finger manipulation during defecation, it is not possible to diagnose patients with FDD based on the presence or absence of these symptoms [6–9]. Therefore, FDD should be diagnosed by both considering the symptoms and physiological testing. The diagnostic criteria for FDD are described in Table 17.2, which are subdivided into inadequate defecatory propulsion and dyssynergic defecation (DD) [10]. In the Rome III criteria, there was a prerequisite to satisfy the diagnostic criteria for FC in order to diagnose FDD. However, the Rome IV criteria include all cases that satisfy the diagnostic criteria for FC or IBS-C or IBS with mixed bowel habits (IBS-M) [10]. The changes in the prerequisites of these diagnostic criteria were based on the research findings that IBS may be related to pelvic floor dysfunction [11, 12] and patients with FDD can be effectively treated through biofeedback treatment regardless of the presence or absence of IBS symptoms [13].

Table 17.1 Rome IV diagnostic criteria for functional constipation (adapted from Lacy et al. [2])

Functional constipation[a]
1. Must include two or more of the following[b]:
a. Straining during more than one-fourth (25%) of defecations
b. Lumpy or hard stools (BSFS 1_2) more than one-fourth (25%) of defecations
c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)
f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
[b]For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these two conditions might overlap

Table 17.2 Rome IV diagnostic criteria[a] for functional defecation disorders (adapted from Rao et al. [10])

1. The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation
2. During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by two of the following three tests:
a. Abnormal balloon expulsion test
b. Abnormal anorectal evacuation pattern with manometry or anal surface EMG
c. Impaired rectal evacuation by imaging
Subcategories F3a and F3b apply to patients who satisfy criteria for functional defecation disorders
F3a. Diagnostic criteria for inadequate defecatory propulsion Inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor muscles[b]
F3b. Diagnostic criteria for dyssynergic defecation Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation[b]

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis
[b]These criteria are defined by age- and sex-appropriate normal values for the technique
EMG electromyography

17.3 Epidemiology and Prevalence of Functional Constipation

In a systematic literature review, the global prevalence of constipation was about 14% (95% confidence interval [CI], 12–17%) and varied by region, with a relatively low prevalence in Southeast Asia [14]. The study results on the prevalence of constipation are reported in various ways according to the constipation diagnostic criteria applied, and recently, the prevalence of constipation using the Rome IV criteria in the United States was reported to be about 24% [15]. The prevalence of constipation was higher in women than in men (odds ratio [OR] 2.22; 95% CI, 1.87–2.62) [14].

The prevalence of constipation increases with age [16, 17]. In a Chinese study using the Rome III criteria, the prevalence of constipation in the population aged 60 years or older was 32.6% (634/1942) and increased with age, and it was found to be 44.8% in those aged 80 years and older [18]. As age increases, intestinal function may decrease, including incomplete relaxation of the rectoanal angle, an increase in perineum descent, a decrease in elasticity of the rectal wall due to decreases in muscle mass and elasticity, and damage to the vulvar nerve. In addition, the incidence of constipation increases due to a combination of factors such as an increase in various underlying diseases including the nervous and endocrine system, increases in medications, changes in dietary intake, and a decrease in physical activity [16, 19]. In a Finnish study, constipation was diagnosed in 57% and 64% of older women and men, respectively, and increased to 79% and 81%, respectively, in the residents of nursing homes [20]. The difference in the prevalence of constipation between men and women disappears with increasing age, and this phenomenon may be due to changes in physical and psychological factors such as female hormones, sociocultural role changes, and underlying diseases that accompany increasing age.

17.4 Symptoms of Functional Constipation

The FC symptoms reported by patients differ according to gender. In a study of constipation patients who visited a tertiary hospital, women showed infrequent bowel movement (adjusted OR [AOR] 2.07; 95% CI, 1.67–5.28), hard stools (AOR 3.08; 95% CI, 1.80–5.28), and longer duration of constipation symptoms (AOR 2.00; 95% CI, 1.05–3.82) than men [21]. In addition, women had an increased frequency of the occurrence of abdominal pain (AOR 2.22; 95% CI, 1.22–4.05), bloating (AOR 2.65; 95% CI, 1.50–4.70), unsuccessful attempts at evacuation (AOR 1.74; 95% CI, 1.01–3.00), and the use of anal digitation to evacuate stool (AOR 3.37; 95% CI, 1.15–9.90) than men [21]. In another study, the frequency of excessive straining during defecation or the feeling of incomplete evacuation was higher in female patients with constipation than males [22]. A previous study reported that the symptoms of DD were associated with the absence of an urge to defecate in men and straining during defecation in women [23]. However, research on whether the symptoms of FC actually differ between men and women is still limited.

17.5 Pathophysiology of Functional Constipation

The main mechanisms of FC are sensorimotor impairment in the large intestine and pelvic floor dysfunction. In addition, various causes such as changes in the microbiome and anatomical structure abnormalities may be involved in the occurrence of constipation. In particular, differences in the effects of sex hormones and brain activity in men and women with constipation have been reported.

17.5.1 Sensorimotor Impairment of the Large Intestine

Normal movement of the colon is characterized by segmental and peristaltic contractions. These

movements occur through the myenteric plexus, interstitial cells of Cajal, and neurotransmitters. Serotonin (5-hydroxytryptamine, 5-HT) is an important representative neurotransmitter that induces local reflexes by releasing stimulatory or inhibitory neurotransmitters such as acetylcholine or nitric oxide through intestinal neurons [24]. In STC, colonic transit time increases, and the frequency of high-amplitude propagating contractions decreases [25]. The physiological and immunohistochemical findings in STC included abnormal colon propulsion activity, delayed proximal colon transit, decreased cholinergic response, increased adrenergic response, weakened gastrointestinal reflex, an incongruity in rectal sigmoid activity, neurodegeneration of the myenteric plexus ganglia and interstitial cells of Cajal, and abnormalities in intestinal neurotransmitters [26]. There are insufficient studies on whether the difference in these changes exists in male and female constipation patients.

17.5.2 Pelvic Floor Dysfunction

Pelvic floor dysfunction is the main cause of FDDs and is caused by a combination of decreased rectal evacuation and resistance to the defecation process. Resistance to the defecation process is caused by high anal resting pressure and paradoxical contractions or incomplete relaxation of the pelvic and external anal sphincters. FDDs are classified into dyssynergic defecation, in which the pelvic floor muscles contract inappropriately during attempted defecation, and inadequate defecatory propulsion, in which there are inadequate propulsive forces [10]. FDDs may be accompanied by decreased rectal sensations. Decreased rectal sensations can reduce the urge to defecate, and in about 50% of these patients, colonic motility is slowed. Retained feces can also physically block the defecation pathway and induce rectocolonic inhibitory reflexes. Over time, excessive straining can weaken the pelvic floor muscles, increasing the risk of excessive perineal descent, rectal prolapse, and isolated rectal ulcer syndrome.

In the anorectal function test, men with constipation had higher median sphincter resting pressures (81.2 vs. 75.2 mm Hg, $p = 0.01$) and mean squeeze pressure (257.0 vs. 170.5 mm Hg, $p < 0.0001$) compared to women with constipation [22]. Men showed less severe straining and incomplete evacuation than women but had greater mean rectoanal pressure differentials (−106.7 vs. −71.1 mm Hg, $p < 0.0001$), a lower mean defection index (0.17 vs. 0.27, $p = 0.03$), and higher volume threshold for urgency (115.2 vs. 103.4 mL, $p = 0.03$). Women were more likely to have abnormal balloon expulsion time than men. In a multivariate analysis, male gender was the only independent predictor of a normal balloon expulsion time [22]. The results of the anorectal function tests suggest the possibility that there is a difference between men and women in the pathophysiology of FC. However, physiological testing, such as anorectal manometry and the balloon expulsion test, should be interpreted with caution as there is a possibility of false-positive results when the patient is uncomfortable.

17.5.3 Influence of Sex Hormones

Female sex hormones affect colon motility and were thought to be one of the causes of STC. In a study on healthy Korean adults, the study found a difference in the colon transit time according to the menstrual cycle, and the colonic transit time in the luteal phase was longer than that in the follicular phase (40.9 ± 19.0 h vs. 20.6 ± 19.2 h, $p < 0.05$) [27]. In a study of pregnant women in China using the Rome III diagnostic criteria for constipation, the prevalence of constipation among pregnant women was 13.0%, which was higher than 6.0% in the general population [28, 29]. As maternal age increased, the prevalence of constipation also increased, especially in pregnant women over 35 years of age, in which it increased to 22.5% (OR 3.010; 95% CI, 2.224–4.076) [29]. These findings suggest that among the female sex hormones, progesterone, in particular, may be involved in STC. However, another study did not report a similar association between the menstrual cycle and colon transit [30], and some studies found that

serum progesterone levels were normal in women with STC [31]. These results indicate that the increased progesterone levels in patients with STC may affect the action mechanism rather than directly affecting intestinal motility, and studies supporting these results have been reported. In the colonic epithelial cells of women with STC, progesterone receptors were overexpressed, serotonin transporter (SERT) levels were lower, and serotonin levels were higher than in healthy women [32]. In epithelial cells, progesterone treatment decreased serotonin transporters and increased mucosal serotonin [32]. Serotonin signaling abnormalities are related to the overexpression of progesterone receptors produced in human epithelial cells, and increased serotonin levels in patients with constipation may appear as a compensatory mechanism for increased colon transit time.

17.5.4 Differences in Brain Activity

It has been reported that brain activity in patients with IBS differed according to gender in functional magnetic resonance imaging [33, 34]. There are few reports of differences in constipation symptoms between men and women. However, like IBS, FC is a functional disease that occurs twice as often in women than in men, so there is a possibility that there is an important difference in the signaling system involved in the visceral stimulus response and emotion regulation processes [35]. The orbital frontal cortex (OFC) and insula (INS) belong to the emotional arousal network mainly involved in regulating visceral responses as emotional processes. The OFC shares extensive connections with areas such as the prefrontal region, limbic system, motor, and primary sensations. The insula is involved in visceral pain, integrating information from the body and internal organs. The lateral OFC is involved in downregulating emotional responses [36], and the insula is mainly involved in integrating emotional information with the gut [37]. In a recent study, abdominal pain and abdominal distension were correlated with transit and state anxiety ratings in female than male patients with FC. The female FC group had lower amplitudes of low-frequency fluctuation (ALFF) than males in the precentral gyrus (PreCen), thalamus (THA), INS, and OFC ($p < 0.01$). ALFF in the INS and OFC was correlated with abdominal pain and difficulty in defecation, respectively, in the female FC group [35]. The positive correlation between the difficulty in defecation and ALFF in the OFC indicates that constipation symptoms have a greater effect on the OFC in female patients with constipation than in male patients. There were also gender differences in resting-state functional connectivity (RSFC) between the INS and lateral OFC (lOFC). The RSFC between the INS and lOFC was weaker in female patients with constipation than in male patients. These findings suggest that the INS and OFC play important roles in modulating the intrinsic functional connectivity of the resting brain networks in patients with FC and that this role is influenced by sex [35] (Fig. 17.1). In this study, male patients with constipation showed higher connectivity between the INS and lOFC than healthy males, reflecting increased responses to persistent visceral stimulation. However, this ability may worsen as abdominal distension increases, which is explained by an inverse correlation between abdominal distension and INS-lOFC connectivity in male patients with constipation. In contrast, INS-lOFC showed lower connectivity and an inverse association with anxiety in female patients with constipation compared to healthy women, suggesting that it may impair the ability to control negative emotional responses in female patients with constipation.

Overall, female patients with constipation had lower INS-lOFC connectivity than male patients and an inverse correlation between the RSFC in INS-lOFC and anxiety/abdominal distension. These findings suggest that the lack of an ability to control visceral sensation and negative emotions in women compared to men may be related to the higher prevalence of constipation in females [35].

17.5.5 Changes in Gut Microbiome

Imbalances in intestinal microflora are known to be involved in the development of functional

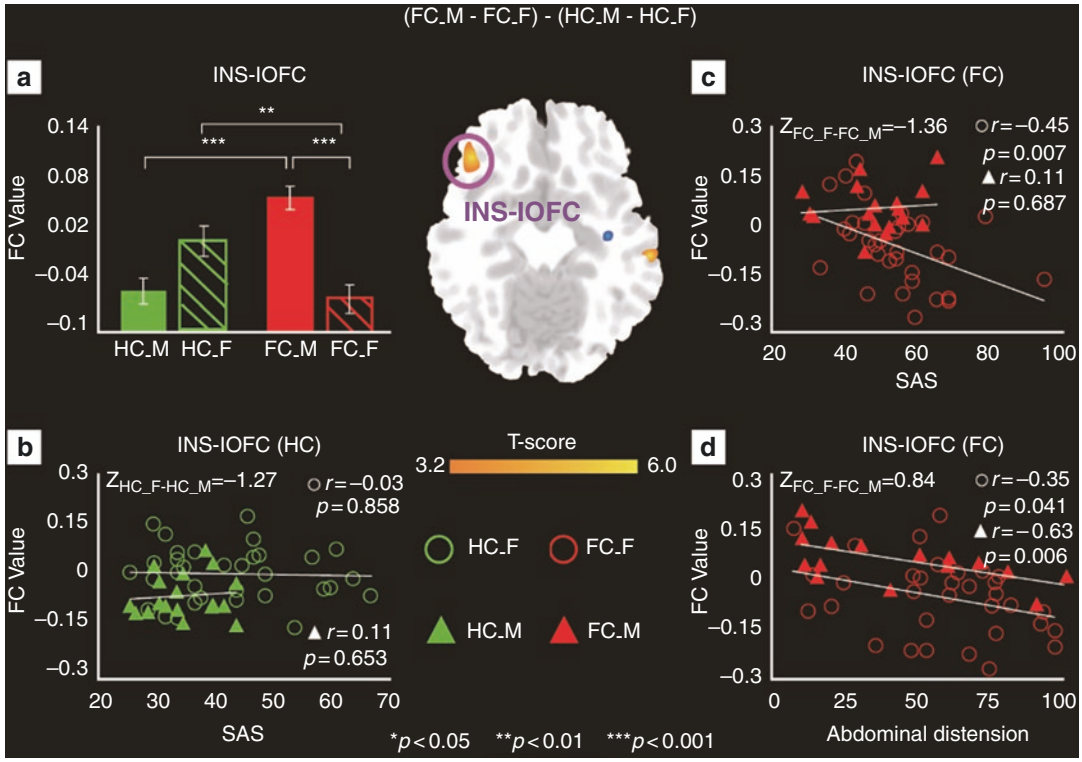

Fig. 17.1 Differences in brain activity between men and women in healthy and constipated patients. (**a**) RSFC strength between the INS and the lateral OFC (lOFC). Male constipation patients showed higher strength of RSFC than healthy male and female constipation patients, and female constipation patients showed lower strength of RSFC than healthy females. (**b**) SAS and RSFC were not correlated in healthy men and women. (**c**) SAS tended to be correlated with RSFC strength between INS and lOFC in female constipation patients, but not in male constipation patients. (**d**) Abdominal distension was inversely correlated with the connectivity between INS and lOFC in male constipation patients, but not in female constipation patients. Z score indicated there were no statistical differences of correlation coefficient between HC_M and HC_F and between FC_M and FC_F. *ALFF* amplitude of low-frequency fluctuation, *FC* functional constipation, *FC_F* female patients with functional constipation, *FC_M* male patients with functional constipation, *HC* healthy control, *HC_F* female healthy controls, *HC_M* male healthy controls, *INS* insula, *OFC* orbital frontal cortex, *RSFC* resting-state functional connectivity, *SAS* self-rating anxiety scale (adapted from Jin et al. [35])

bowel diseases such as IBS. Changes in gut microflora have also been reported in patients with FC [38]. Khalif et al. reported that *Bifidobacterium*, *Lactobacillus*, *Clostridium*, and *Bacteroides* were decreased and *Escherichia coli*, *Enterobacteriaceae*, and *Staphylococcus aureus* were increased in stool microbial cultures of patients with constipation [39]. In a Korean study, stool analysis using real-time quantitative polymerase chain reaction (qPCR) showed that *Bifidobacterium* and *Bacteroides* were decreased in patients with constipation compared to healthy adults [40]. Another study examining microbial changes in the colonic mucosa reported that the colonic mucosa of patients with constipation was particularly rich in *Bacteroides* compared to normal individuals and that this difference had an accuracy of 94% [41]. In patients with constipation, changes in gut microflora are still inconsistent. The putative microbiotic-dependent mechanisms in chronic constipation are shown in Fig. 17.2 [42]. Intestinal microorganisms affect intestinal motility by participating in the development of the enteric nervous system (ENS), the synthesis of short-chain fatty acids (SCFAs), and the metabo-

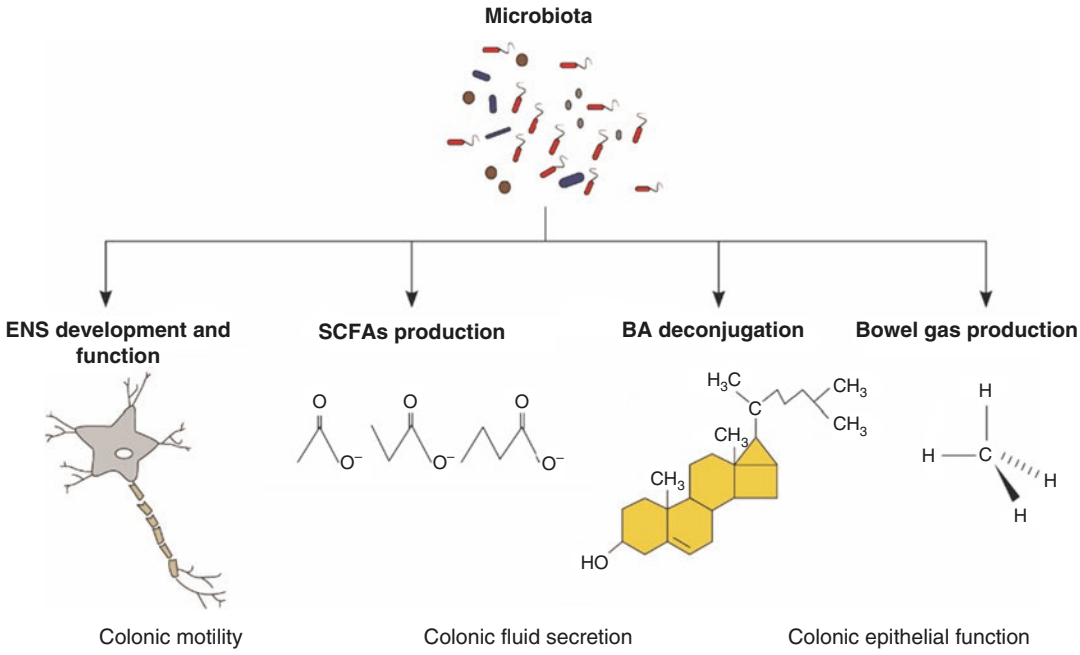

Fig. 17.2 Putative microbiotic-dependent mechanisms in chronic constipation. *BA* bile acids, *ENS* enteric nervous system, *SCFAs* short-chain fatty acids (adapted from Kaminski et al. [42])

lism of bile acids [43]. The ENS is involved in intestinal motor and sensory functions through reflex pathways that can function independent of the central nervous system [44]. Metabolites such as SCFAs or peptides generated during fermentation by intestinal microbiota can stimulate ENS and affect intestinal motility [45]. The gut neuroendocrine system interacts with the gut microbiota via serotonin [46]. Serotonin is produced in the ENS and central nervous system and plays a central role in mediating motor and sensory responses in the ENS. Serotonin stimulates local enteric nerve reflexes to initiate secretion and propulsion and acts on the vagus afferent nerve to control contractile movements [47]. Slow bowel movements are aggravated when the amount of serotonin in the large intestine decreases. It is also associated with a relative decrease in *Firmicutes*, an increase in *Bacteroides*, and changes in SCFAs and bile acids in the stool [48]. There are still few studies on the differences between men and women in the distribution of intestinal microbiota in patients with constipation, so further research is needed.

17.6 Treatment of Functional Constipation

The first step in the treatment of FC is to improve lifestyle and diet, and if necessary, appropriate laxatives are administered. Laxatives include bulking laxatives, osmotic laxatives, stimulant laxatives, prokinetics, and secretagogues. Studies on the therapeutic effect of laxatives have been unable to prove a difference between men and women because the study subjects were mostly female patients. Although laxatives can improve FDD, biofeedback treatment is very effective in this subgroup.

17.6.1 Diet and Lifestyle Modification

Adequate dietary fiber intake is important in patients with constipation. Dietary fiber can improve constipation symptoms by increasing stool volume and softening it and increasing the frequency of defecation. Most guidelines rec-

ommend consuming 20–25 g of fiber per day [49]. In a meta-analysis, dietary fiber increased bowel frequency in patients with constipation, but it was not clear whether it could improve stool hardness or reduce the use of laxatives [50]. In some severely constipated patients, excessive fiber intake may cause abdominal distension, so it should be consumed with caution [50]. Another study found that a vegetarian diet rich in fruits and vegetables for 12 weeks reduced the number of patients complaining of constipation [51].

Constipation patients are advised to drink 1.5–2 L water per day. A National Health and Nutrition Examination Survey in the United States showed that bowel frequency decreased and stool became firmer as water intake decreased regardless of gender, suggesting a possible association between constipation and water intake [52]. There is still no evidence that increased fluid intake is effective in treating constipation, but it may help in treating constipation in patients with insufficient fluid intake [53, 54]. As suggested in the Korean guidelines, when taking bulk-forming laxatives, sufficient fluid intake is recommended in consideration of the mechanism of action [49].

The effects of physical activity vary in the treatment of constipation. Regular aerobic exercise (e.g., walking and cycling) can be effective for constipation by shortening the overall colon transit time and the rectosigmoid colon transit time [55]. In a study, moderate-to-high physical activity shortened the colon transit time only in women with constipation [56]. Although there is still no evidence that physical activity is effective in treating constipation, it is recommended for patients with constipation because it can improve the quality of life and provide health benefits.

In summary, dietary studies related to constipation still lack evidence and do not have the same effect on all patients with constipation, so it is desirable to eat a balanced diet along with appropriate physical activity for the treatment of constipation. It is helpful to relatively increase the intake of foods high in fiber and drink sufficient water to ensure adequate hydration.

17.6.2 Laxatives

Bulking laxatives absorb water in the large intestine to increase stool volume, shorten colon transit time, and soften stool so that it can be easily evacuated. Compared to placebo, bulking laxatives (especially psyllium) improved overall constipation symptoms, such as straining, pain during defecation, and stool hardness, and increased the number of bowel movements per week [57]. The Korean guidelines state that bulking laxatives are effective in the treatment of chronic constipation and can help patients with chronic constipation with inadequate fiber intake [49]. Bulking laxatives are relatively safe drugs with few side effects, but when they are fermented by bacteria in the colon, gases such as hydrogen, methane, and carbon dioxide are generated, so they can cause abdominal distension, bloating, and gas, which can lead to poor compliance with the drugs. For this reason, it is recommended to gradually increase the dosage of bulking laxatives. Bulking laxatives are ineffective in severe STC, DD, fecal impaction, and drug-induced constipation and may worsen symptoms, so it is preferable to use osmotic laxatives first [58]. Osmotic laxatives are not absorbed from the intestine but move body water into the intestinal lumen by osmotic pressure to facilitate defecation. Osmotic laxatives are divided into magnesium laxatives, non-absorbable polysaccharides, and polyethylene glycol (PEG). Magnesium laxatives are widely used because they are inexpensive and easy to take and they improve bowel frequency and stool consistency, but studies on magnesium laxatives are lacking. In particular, if there is a decrease in renal function or neuromuscular disease, magnesium laxatives may induce hypermagnesemia, resulting in a gradual loss of neuromuscular, respiratory, and cardiac function. They can cause hypotension and conduction abnormalities, which may lead to bradycardia and even cardiac arrest [59]. The Korean guidelines recommend that they should not be used in patients with impaired renal function as it may cause hypermagnesemia [49]. Non-absorbable polysaccharides include lactulose and lactitol, and PEG includes PEG 3350 and

Macrogel 4000. Non-absorbable polysaccharides are not absorbed in the small intestine but are metabolized by bacteria in the large intestine and converted to fatty acids to increase osmotic reactions and stimulate colonic motility. Non-absorbable polysaccharides have the advantage that they are not absorbed into the bloodstream, so there is no risk of their systemic circulation. In a study of patients with FC, when lactulose was taken at 45–60 mL per day, the transit time in the proximal colon was accelerated, bowel frequency increased, stool hardness improved, and the overall symptoms related to constipation improved [60]. PEG is a high molecular weight polymer that is not absorbed in the intestine and remains in solution to maintain high osmotic pressure in the large intestine. It does not absorb water into the body, so it softens stool consistency and increases stool amount. In a meta-analysis, the number of bowel movements per week increased by 1.98 times in the constipated group taking PEG compared to the placebo group, and the hardness and ease of defecation were also improved [61]. According to the Korean guidelines, non-absorbable polysaccharides and PEG are effective drugs for improving the frequency and hardness of bowel movements in patients with chronic constipation [49]. These drugs have few serious side effects, so can be administered for the long term, and are recommended for elderly patients with chronic constipation [49]. Non-absorbable polysaccharides may cause abdominal distension and flatulence due to gas produced by metabolism by bacteria in the large intestine. In contrast, PEG does not undergo a metabolic process and does not generate gas, so it has higher compliance than non-absorbable polysaccharides. PEG may be more effective than non-absorbable polysaccharides in patients with severe abdominal distension or gas. Since both drugs take effect 24–72 h after taking them, the patient should be informed of this, and the dose should be increased slowly [62].

The stimulant laxatives include anthraquinones (senna, cascara, and aloe), polyphenols (bisacodyl and phenolphthalein), and surfactant laxatives (docusate, castor oil, and dehydrocholic acid). Most stimulant laxatives are composed of multiple ingredients rather than a single ingredient. Although the exact mechanism of action is not known, stimulant laxatives are considered to promote intestinal movement by inhibiting the absorption of water and electrolytes in the large intestine and stimulating the muscular plexus. They can cause cramping pain and diarrhea, and long-term use can cause electrolyte and water abnormalities such as hyponatremia, hypokalemia, dehydration, secondary aldosteronism, steatorrhea, cathartic colon, and protein-loss enteritis [63, 64]. The safety has not been established for use for more than 4 weeks.

Prucalopride is a selective type 4 serotonin receptor agonist that directly promotes gastrointestinal motility. In an analysis of six case-control studies, the group administered prucalopride at 2 mg had a higher frequency of three or more spontaneous bowel movements a week for 12 weeks compared to the control group and showed high safety and compliance. There was no difference in the efficacy and safety of prucalopride between men and women [65]. Prucalopride is administered at 2 mg once a day. The administration of 1 mg once a day is recommended for elderly patients 65 years of age or older and patients with severe renal impairment (glomerular filtration rate of <30 mL/min/1.73 m^2) and severe hepatic impairment (Child-Pugh class C). Although it is relatively safe, headache is most common on the first day of use and improves gradually. Giving patients this information can help improve their adherence to the drug. Unlike non-selective type 4 serotonin receptor agonists such as cisapride and tegaserod, prucalopride selectively acts only on type 4 serotonin receptors, so no cardiovascular side effects have been reported.

Laxatives are selected in consideration of the patient's overall condition, such as age and underlying disease, and either bulking or osmotic laxatives are selected first. Bulking laxatives may be preferentially selected over osmotic laxatives in patients whose colonic transit time is judged to be close to normal due to insufficient dietary fiber intake. That is, if the patient defecates less than one to two times a week, the stool form is Bristol stool form scale 1 or 2, and stool retention is sus-

pected in simple abdominal X-ray, it is better to select an osmotic laxative rather than a bulking laxative. Osmotic laxatives should be selected in consideration of the advantages and disadvantages of the drugs. Magnesium salt is inexpensive, is easy to take, and has the advantage of showing quick effects, so it can be selected for patients without renal impairment or neuromuscular disease. Non-absorbable polysaccharides and PEG have few serious side effects and can be administered for a long period of time, so they can be prescribed first for elderly patients or patients with accompanying underlying diseases [66]. The choice between the two drugs takes into account compliance, accompanying symptoms such as gas or abdominal distension, and cost. PEG may be effective if it is difficult to take due to the sweet taste of non-absorbable polysaccharides or if gas or abdominal distension is severe. PEG can rarely cause electrolyte imbalance and water retention if taken in excess, so it should be used with caution when kidney or heart function is impaired [58]. When prescribing prucalopride, age, renal function, and liver function must be checked before administration, and excessive doses must be avoided. Cardiovascular adverse events have not yet been reported, but caution is warranted in patients at risk for cardiovascular disease [62]. It has not yet been determined in what order and in which combination laxatives should be used when a patient does not respond to one laxative. The choice of laxative should be selected in consideration of the patient's symptoms, underlying disease, period of time required for treatment, administration interval, drug characteristics, effects, side effects, and long-term safety, as well as the economic aspects. When the laxative being taken is ineffective, it may be more effective to add another drug with a different mechanism of action that does not increase side effects rather than increasing the dose of the drug over the standard therapeutic dose [67].

17.6.3 New Laxatives

Lubiprostone is a chloride channel activator that induces intra-intestinal water and chloride secretion and accelerates transit [68, 69]. In randomized controlled trials (RCTs) in patients with chronic constipation and IBS-C, lubiprostone was associated with significantly improved symptoms [69–72]. Lubiprostone may cause nausea and has been suspected to promote abortion rates in animal studies due to its prostaglandin properties [69]. Hence, it is mostly used as a reserve medication and has not yet been approved in most European countries. Linaclotide acts as an oral guanylate cyclase C receptor agonist and increases intracellular cyclic guanosine monophosphate (cGMP) levels. Thus, fluid secretion into the intestinal lumen is increased, which, in turn, accelerates gastrointestinal transit velocity [73, 74]. In recent European guidelines, lubiprostone and linaclotide were effective in the management of chronic constipation and IBS-C [75].

17.6.4 Biofeedback Therapy

Biofeedback therapy is an effective method for the treatment of DD, which can be safely and repeatedly performed and can reduce the use of laxatives [49]. Biofeedback therapy is a process of retraining the anorectal and pelvic muscles of patients with constipation. Biofeedback therapy is effective in about 70% of the patients with DD and lasts for more than 2 years but has little effect in patients with STC [76, 77]. Although patients with DD can be treated with laxatives, it is desirable to recommend biofeedback therapy regardless of the laxative response. It is predicted that biofeedback therapy will be more effective in patients with hard stools, shorter duration of laxative use, high resting sphincter pressure, and longer balloon expulsion time [78]. Biofeedback therapy can be recommended for these patients.

17.6.5 Surgical Treatment

Colectomy may be helpful in the treatment of patients with STC who do not have defecatory dysfunction and do not respond to laxatives. Surgical treatment can also be effective in patients with outlet obstruction such as symptomatic rec-

tocele and rectal prolapse [49]. However, research on the surgical treatment of FC is still lacking [79]. Surgical treatment can result in serious complications, so it should be considered carefully and selectively in patients with STC who do not respond to non-surgical treatment and do not have DD.

17.7 Conclusions

The prevalence of FC is about twice as high in women as in men. Women with FC had more infrequent bowel movements, hard stools, unsuccessful attempts at evacuation, and used anal digitation to evacuate stool than men. And the duration of symptoms was longer, and the frequency of abdominal pain or bloating was higher in women with constipation than in men. However, studies on whether the symptoms of constipation actually differ between men and women are limited. Women with STC were reported to have abnormalities in the serotonin signaling system, suggesting that STC is related to the overexpression of progesterone receptors rather than the direct effect of progesterone. Also, in female constipation patients, changes in brain activation, which are expected to decrease the ability to control the signaling system involved in visceral sensations and emotional responses, have been reported. This difference may be a factor in increasing the prevalence of constipation in women. Although changes in intestinal microbiota have been reported in patients with FC, studies on the differences between men and women are still insufficient. In the future, it is expected that additional studies will be conducted to identify the differences between constipation in women and men so that they can be used for the tailored treatment of patients with constipation.

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Functional Diarrhea

18

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18.1 Introduction

Diarrhea can be caused by a variety of functional or organic causes. In the case of a chronic course, functional diarrhea, or irritable bowel syndrome (IBS), may be suspected. At the same time, it should be possible to differentiate the causes of various organic diarrheas. In addition to symptomatic treatment, customized prescriptions for organic causes are possible.

18.2 Definition of Diarrhea

It is easy to judge the hardness of stool subjectively, but there is a limit to defining diarrhea without any scale. The Bristol stool scale, which more objectively defines the hardness of the stool, can be applied. In this case, type 6 (soft stools with lumpy edges) or type 7 (watery stools with few lumps) is defined as diarrhea [1]. In addition to stool hardness, diarrhea can be defined by the number of bowel movements or the amount of stool per day. It is generally accepted that the amount of stool in a healthy adult is up to 200 g per day [2]. However, the daily amount of stool can vary greatly depending upon the amount of food ingested and the composition of the diet. Therefore, it is only used for research purposes. Eating a high-fiber diet or overeating can lead to a large increase in stool volume. However, if the stool volume is in the normal range but the firmness is loose or watery, the patient is considered to have diarrhea. An alternative to the definition of stool firmness and volume is the number of bowel movements per day. Generally, three or more bowel movements per day can be defined as diarrhea. As a systematic diagnostic approach for diarrhea has not been established, it can arbitrarily be divided into acute and chronic categories according to the duration of diarrhea. When diarrhea lasts more than 4 weeks, it is defined as chronic diarrhea and is distinguished from acute diarrhea [3]. Occasionally, fecal incontinence may occur alone or be accompanied by diarrhea, and a distinction is required. Fecal incontinence is involuntary defecation and can be caused by damage to nerves or intestinal muscles that act to control defecation. Since severe diarrhea can be accompanied by temporary fecal incontinence, clinicians must differentiate whether the patient's main symptom is diarrhea, diarrhea accompanied by temporary incontinence, or fecal incontinence.

18.3 Epidemiology

Most available epidemiologic and disease burden data relate to IBS. Epidemiologic studies conducted in the USA, the UK, and New Zealand

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showed that about 10–50% of patients with IBS-related symptoms visited medical institutions [4–6]. When analyzing which factors in the patients experiencing changes in bowel habits such as diarrhea were related to the use of medical institutions, the weaker the mental health and social support bases, the higher the visit rate to medical institutions. According to US healthcare statistics, diarrhea remains a major healthcare issue and accounts for more than five million outpatient or emergency room visits annually [7].

According to a large cohort study in the UK using the Rome criteria III questionnaire, which has been validated, the average age of functional diarrhea patients was significantly higher than IBS with predominant diarrhea (IBS-D) patients (mean age 41.8 years vs. 48.2 years old, $p = 0.001$) [8]. In addition, the gender ratio of patients diagnosed with functional diarrhea was also lower compared to that for IBS-D (female ratio 69.5% for IBS-D vs. 50.5% for function diarrhea, $p = 0.001$). Anxiety scales, somatization-type behavioral patterns, higher education levels, and lower body mass index were much more pronounced in IBS-D. What can be confirmed through these epidemiological characteristics is that the two diseases are relatively separate diseases, while the Rome diagnostic criteria are not based on pathophysiology and have the limitation of arbitrary classifications. The ratio of overlap syndrome between IBS-D and functional diarrhea was 27.6%, which was higher than the ratio of overlap syndrome between IBS with predominant constipation (IBS-C) and functional constipation, 18.1%. It can be assumed that the two functional gastrointestinal diseases with diarrhea as the main symptom cannot be sufficiently distinguished as individual diseases by the Rome criteria [8].

In a cross-sectional study using phone interviews to confirm the percentage of the population who experienced diarrhea in the past 4 weeks based on the number of bowel movements, the prevalence was high in women in all countries (4.2–9.0% for women; 2.7–7.2% for men), and the prevalence decreased with increasing age [9]. Considering the definition of diarrhea in that study, both acute and chronic diarrhea could be included, but the results were consistent with the epidemiologic pattern of general IBS. In contrast, in a cross-sectional study in Beijing, there was no difference in the proportion of male and female patients who experienced diarrhea for 1 year. There was a difference in the prevalence according to behavioral patterns such as hand-washing behavior, uncooked food intake habits, cooking utensil use habits, and exercise habits [10]. These are the main risk factors for acute infectious diarrhea. Combining the two studies described above, a difference in prevalence by sex could be confirmed when IBS was the chief possible diagnosis, and no sex difference in the prevalence of diarrhea was found in the group where acute infectious diarrhea was the main possible diagnosis.

18.4 Symptomatology

If diarrhea persists for more than 4 weeks, the clinician can presumptively rule out infectious diarrhea (rarely *Yersinia* or *Campylobacter* infections) and suspect the possibility of IBS-D or functional diarrhea. If symptom-based diagnostic methods (Manning criteria and Rome criteria I, II, and III) were prioritized for patients with IBS symptoms, the positive likelihood ratios were 2–3, and the negative likelihood ratios were at the level of 0.2–0.6 by meta-analysis [11]. A diagnosis based on symptoms is basically a diagnosis of exclusion. The likelihood ratio of a diagnosis using biomarkers was compared by meta-analysis. The method with the best positive likelihood ratio was 26.4 (95% CI, 11.4–61.9) when using fecal calprotectin, intestinal permeability, and the Rome criteria I [11]. The most obvious method for the negative likelihood ratio was to use serum biomarkers and psychiatric measures, and the likelihood ratio was 0.18 (95% CI, 0.12–0.25) [11]. Thus, these biomarker-supported diagnoses were superior to symptom-based diagnoses, but these markers are not generally used in clinical practice. In the future, it can be expected that appropriate tests to supplement the symptom-based diagnostic method will overcome the limitations of the Rome criteria.

For chronic diarrhea patients who show one or more alarm features (e.g., unintentional weight loss, blood in the stool, nocturnal diarrhea, and unexplained iron deficiency anemia), whether they have been screened for colorectal cancer according to their age needs to be checked. However, in countries with poor access to medical care, data that question the usefulness of alarm features have been presented [12, 13]. As a result of a study of 2000 people who recently visited secondary medical institutions, the sensitivity of alarm features to colorectal cancer was very limited at 2–33% [14]. Therefore, where medical accessibility is very good, it is desirable to check the age-appropriate colorectal cancer screening history even if there is no alarm feature in a patient complaining of chronic changes in bowel habits such as diarrhea.

Regardless of accessibility to medical care, it may be an effective approach for patients with diarrhea to suspect organic disease as non-invasively as possible. Data on inflammatory bowel disease (IBD) rates in patients presumptively diagnosed with IBS in the USA and Canada were significantly different at 0.4% and 11%, respectively [15]. This was largely due to the difference in the composition of the referred patients. A representative example that can objectively quantify the presence of intestinal inflammation in clinical practice is fecal calprotectin. A high-quality literature review revealed that a fecal calprotectin level of less than 50 μg/g excluded the presence of IBD with the best sensitivity, good specificity, and low false negatives in patients complaining of chronic diarrhea [3].

18.5 Pathophysiology of Diarrhea

18.5.1 Overview

Diarrhea is the main defense mechanism of the digestive tract, and it maintains the health of the human body by rapidly discharging toxins or microorganisms ingested orally. However, it causes discomfort due to inappropriate symptoms through a chronic course, and its meaning as a defense mechanism is diluted. Alterations in the regulation of water in the intestinal tract, along with changes in intestinal motility, are the main mechanisms of diarrhea. The water-binding ability of insoluble stool substances (e.g., dietary fiber and bacterial cell walls) has been suggested as a major factor in determining stool hardness [16]. Soft stools occur when insoluble stool material has a low capacity to bind water compared to existing water, and solid stools occur when the capacity is sufficient. Therefore, stool hardness is determined by the ratio between the amount of water present in the intestinal tract and the water-binding capacity of the insoluble stool material. In other words, it cannot be said that diarrhea occurs just because there is a lot of water in the lumen, and it is also the basis for not being able to define diarrhea only by the amount of feces. However, in most cases, changes in the amount of water present in the intestinal tract are more important than changes in the water-binding capacity of insoluble fecal material. The total amount of water ingested per day, saliva, gastric acid, pancreatic juice, and digestive juices secreted into bile is about 10 L, of which 8–8.5 L is absorbed in the small intestine [2]. The amount of water passing through the cecum is about 1.5 L, and the amount of water excreted per day is only about 0.1 L as most of it is absorbed by binding with insoluble fecal material in the intestinal tract or passing through the large intestine, 1.4 L. The amount of unabsorbed water in the intestinal tract increases by only 1% per day, and diarrhea is induced even when the amount of water in the intestinal tract becomes 0.2 L. The function of epithelial cells, which are the main mechanisms that control the amount of water in the intestinal tract, and changes in the secretion of digestive juices are involved in the occurrence of diarrhea, and in most cases, these two problems co-exist.

18.5.2 Specific Diagnosis of Chronic Diarrhea

18.5.2.1 Bile Acid Diarrhea

Bile acid is synthesized in the liver and secreted into the bile after meals to aid in the absorption of

fat-soluble nutrients. About 95% of the secreted bile acids are reabsorbed in the terminal ileum to control the amount of bile acid synthesis in the liver. Bile acids inhibit the growth of some gut microbiota or promote intestinal movement, and the presence of high concentrations of bile acids in the large intestine may cause diarrhea. A high concentration of bile acids may be generated in the intestinal tract due to a problem with the gene involved in preventing the normal feedback inhibition of bile acid synthesis or by inhibiting the absorption of bile acids due to surgical resection of the terminal ileum [3]. The amount of bile acid synthesized can be measured by SeHCAT, a nuclear medicine test using ^{75}selenium. Since this modality is not practical, it is usually diagnosed by confirming an improvement in diarrhea after the empirical prescription of bile acid resin (cholestyramine).

18.5.2.2 Small Intestinal Bacterial Overgrowth

The main symptom of small intestinal bacterial overgrowth (SIBO) is chronic diarrhea. Hypoacidity, the long-term use of drugs that decrease intestinal motility, diabetic neuropathy, and a history of gastrointestinal surgery are the main causes of SIBO [17]. The diagnostic criterion for SIBO is the presence of 10^5 or more bacteria per 1 mL of fluid of the jejunum, and it is usually determined by a non-invasive test (hydrogen breath test). When bacteria in the small intestine become chronically excessive, as described above, the defense mechanism of the digestive tract is activated, or the water-binding ability of insoluble fecal substances (such as bacteria cell walls) that determines the hardness of feces is changed, which can cause diarrhea.

18.5.2.3 Microscopic Colitis

The long-term intake of drugs such as vitamins, statins, or nonsteroidal anti-inflammatory drugs can change the absorptive function of epithelial cells, and diarrhea can be caused by the infiltration of lymphocytes into the intestinal tract or the deposition of collagen beneath the intestinal epithelial cells. Unlike IBD, inflammation does not spread to glandular structures. It can occur at any age, but it is more common in people over the age of 60. Although nonspecific findings including minimal edema, redness, and erosion of the mucous membrane can be observed by colonoscopy, in many cases, the mucosa appears to be normal. Therefore, random biopsies are performed for each segment of the colon for diagnosis. Because pathological changes in the right colon are more pronounced than those in the left colon, the diagnostic efficiency of sigmoidoscopy is low.

18.6 Medical Treatment of Chronic Diarrhea

Table 18.1 summarizes possible drug treatments for pathological diarrhea.

18.6.1 Loperamide

Loperamide is a synthesized μ-opioid agonist that activates inhibitory presynaptic receptors in the enteric nervous system, thereby inhibiting intestinal peristalsis and inducing a decrease in intestinal secretions. It also has the effect of increasing the pressure of the anal sphincter. This improves the symptoms of loose stools, the urge to defecate, and fecal incontinence in patients with diarrhea. The starting dose is 4 mg per day and can be increased to a maximum of 16 mg per day by additional doses of 2 mg every 4 h [18]. According to a recent Food and Drug Administration (FDA) safety letter, dizziness, palpitations, and dullness may be experienced by an overdose of loperamide, and QT segment prolongation was confirmed in these patients. Therefore, when prescribing loperamide, caution should be exercised in the concomitant administration of other drugs that may prolong the QT segment.

18.6.2 Ramosetron

Serotonin is a neurotransmitter that is involved in euphoria in the brain, and about 90% of it is secreted from the intestinal nervous system in the human body. Serotonin, secreted from the enteric nervous system, is an important neurotransmitter

Table 18.1 Possible drug remedies for chronic diarrhea

	Mechanism	Efficacy	Quality of data	Adverse events	Limitation	FDA end points
Ramosetron	5-HT_3 antagonist	Effective	High	Constipation	Limited number of RCT	NNT 7 Δ = 15% (Alosetron)
Loperamide	μ-Opioid agonist	Unknown	Low	Fatal cardiac arrhythmia on overdose	Limited number of RCT	NNT 10 Δ = 10% (Eluxadoline)
Cholestyramine	Bile acid sequestrant	Unknown	Low		No RCT	
Rifaximin	Non-absorbable antibiotics	Effective	Moderate	Possible risk of antibiotic resistance	Small therapeutic gain	NNT 10 Δ = 9%
Antidepressant	Central sensory modulation	Effective	Moderate	Xerostomia, drowsiness	Quality of RCT issue	
Antispasmodic	Smooth muscle relaxation	May be effective	Low	Xerostomia, visual disturbance	Quality of RCT issue	

RCT randomized controlled trial

involved in the transit time of the colon and visceral pain. The amount of serotonin secreted from the enteric nervous system after a meal was increased in patients with IBS-D [19]. Ramosetron, a serotonin type 3 receptor antagonist, is effective in treating IBS-D by delaying colonic transit time, reducing postprandial gastric-colon reflexes, and lowering rectal irritability [20]. The administration of 5 μg of ramosetron to male patients improved the overall symptoms in IBS-D patients compared to placebo. In contrast, in a placebo-controlled study conducted in female patients, taking 2.5 μg of ramosetron once a day improved abdominal pain and discomfort, stool firmness, and overall symptoms [21, 22]. No serious side effects were reported even with long-term use, and some patients complained of constipation. For female or male patients with mild symptoms, the initial dose can be started at 2.5 μg, and the dosage can be increased according to the clinical course.

18.6.3 Rifaximin

As described above, the main symptom of patients with SIBO is diarrhea. In addition, since about 10% of IBS-D patients may have accompanying bacterial overgrowth in the small intestine, it can be treated with antibiotics that are not absorbed from the intestinal tract. A relatively high daily dose of 1200–1600 mg of rifaximin is recommended for this purpose. The effect was confirmed to last for more than 10 weeks when administered at a high dose [23]. Among rifaximin responders, 64.4% experienced a recurrence of symptoms and improved again when they were given a second dose [24]. Rifaximin is poorly absorbed from the digestive tract, so there are few side effects. However, in consideration of the risk of antibiotic resistance, limiting the administration of rifaximin to refractory patients who have not improved with other drugs is recommended.

18.6.4 Cholestyramine

Since high concentrations of bile acids can cause diarrhea, cholestyramine, a resin of bile acids, can improve diarrhea. Very few medical institutions can perform the SeHCAT test to diagnose bile acid-related diarrhea. Therefore, bile acid diarrhea can be diagnosed if the symptoms improve after the empirical administration of cholestyramine. Cholestyramine also has the effect of improving dyslipidemia.

18.6.5 Tricyclic Antidepressants

Tricyclic antidepressants may be useful in patients complaining of diarrhea by regulating intestinal transit time. In patients with IBS-D, it was confirmed that the symptoms improved regardless of the dose or blood concentration of the tricyclic antidepressant. Rather, the improvement was related to the cognitive aspects (improvement in the number of bowel movements, awareness of symptom control, and confidence in treatment) [25, 26]. Therefore, patients who complain of changes in bowel movements do not need the high doses used for depression but start with a low concentration and maintain it at a level where the frequency of bowel movements is controlled. Clinicians also can adjust the dosage so that systemic side effects such as drowsiness, dry mouth, voiding difficulty, and constipation do not occur. Antidepressants are relatively safe because they do not cause serious side effects, but it is also worth noting that the QT interval may be prolonged. In the case of amitriptyline, it is appropriate to start with 5 mg or less once a day before bed and not exceed 30 mg per day [27].

18.6.6 Antispasmodic Agents

Antispasmodics reduce abdominal pain by suppressing bowel contractions occurring after meal ingestions and improve symptoms by modulating colon transit time. A meta-analysis confirmed that antispasmodics improved the overall symptoms of IBS-D compared to placebo [28]. In addition, there are no serious side effects related to the drug, and it is relatively safe. The drugs that have consistent study results or that satisfy the specific drug efficacy criteria of the FDA are pinaverium, hyoscine, and otilonium bromide [29].

18.7 Conclusions

Diarrhea is the body's defense mechanism, but if it has a chronic course of more than 4 weeks, it can be a pathological problem that causes unnecessary discomfort. Patients with chronic diarrhea may be suspected of having IBS-D or functional diarrhea, but other organic diseases should be excluded. Epidemiology or the treatment of functional diarrhea is limited in its application according to IBS-D. It is necessary to distinguish a special type of chronic diarrhea in which only diarrhea is the main symptom without abdominal pain such as bile acid diarrhea, SIBO, and microscopic colitis. It should be noted that the appropriate dose of a drug differs according to age and sex.

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Inflammatory Bowel Diseases

19

Yonghoon Choi and Nayoung Kim

19.1 Introduction

Inflammatory bowel diseases (IBDs) are a group of idiopathic diseases having a complex pathophysiology, with immune response dysregulation being their main mechanism [1, 2]. The number of IBD patients worldwide is on the rise. The number of IBD patients and medical expenses in Korea also continue to rise significantly, leading to increased disease burden [3]. Risk factors for IBDs include genetic sensitivity [4, 5] and environmental factors such as dietary or antibiotic exposure [6, 7]. Additionally, females are well-known risk factors for IBDs such as Crohn's disease (CD) [8–10]. Although sex differences in the incidence and prevalence of IBDs have not been well known, there have been reports of sex differences, showing that female CD patients have higher disease severity than male patients and that the occurrence of ulcerative colitis (UC) is more commonly observed in males [11]. Recent studies have shown that sex hormones such as estrogen are underlying mechanisms for these sex differences [8–11]. The objective of this chapter is to examine and summarize reported differences in etiologies, mechanisms, symptoms, and treatments of IBDs between males and females reported up to date.

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19.2 Definition and Classification of Inflammatory Bowel Diseases

UC is a chronic inflammatory disease with unknown etiology and is characterized by inflammation confined to the mucosal or submucosal layer of the large intestine with repeated bloody diarrhea, fecal urgency, and abdominal pain [12]. UC is reported to be caused by a combination of genetic and environmental factors [4–7]. It is known to be the most common in North America and Northern Europe [13], although it has been reported worldwide. By race, it is common in Jews and Caucasians, but relatively rare in Asians [13]. However, with the improvement of sanitation, recent outbreaks have continued to rise in southern Europe, Asian countries including South Korea and Japan, and other developing countries [14–17]. Endoscopically, UC is characterized by continuous and symmetrical inflammatory lesions going up from the rectum and invading various ranges depending on the activity of the disease. Inflammation is usually the most severe in the rectum, while the proximal area becomes less so, showing relatively clear boundaries from normal mucosa.

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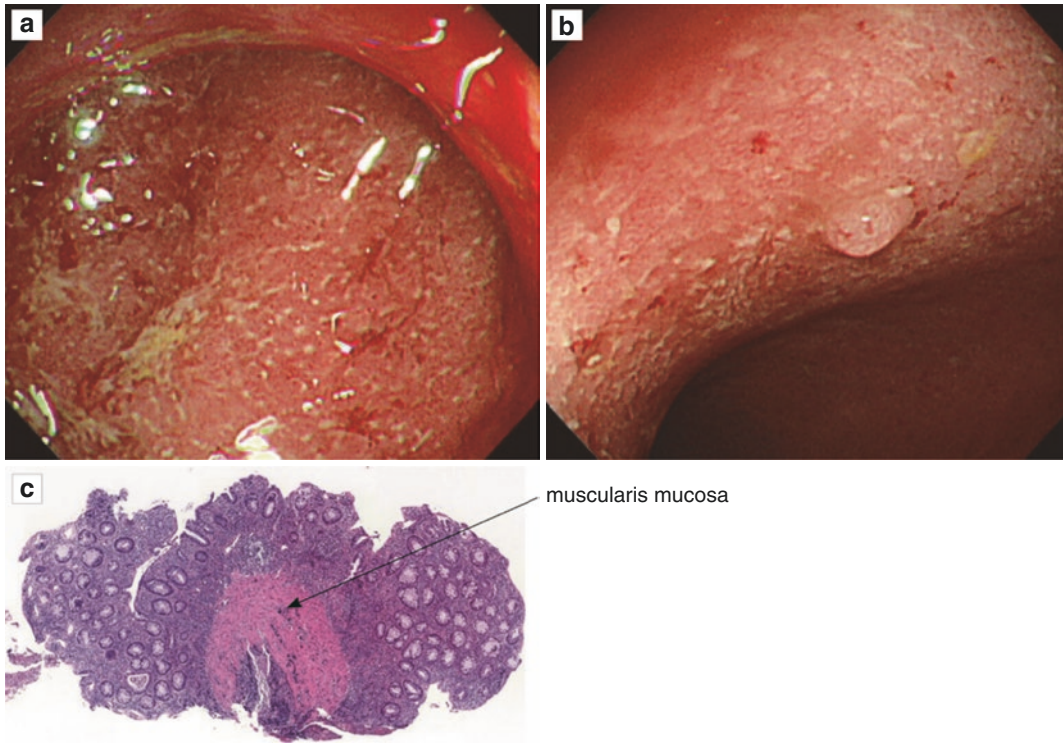

Fig. 19.1 Endoscopic and histologic features of ulcerative colitis. (**a**) Rectal mucosa is covered with inflammatory exudates, with loss of normal vascular patterns due to edematous, hyperemic change observed on endoscopy. (**b**) Granularities are also observed on endoscopy. (**c**) Histologically, inflammation is confined within submucosal layer. Inflammatory cell infiltration with atrophy, structural distortion of crypt, cryptitis, and crypt abscess are observed

In mild to moderate diseases, loss of normal vascular patterns is observed due to edema and loss of transparency in mucosa. In severe cases, large amounts of mucus, changes in mucosal surface with hyperemia, granularity, and friability are shown (Fig. 19.1). The severity of the disease can be assessed by Mayo's Score or Truelove and Witt's Score that depends on clinical symptoms such as diarrhea, hematochezia, and endoscopic findings [18].

CD is a chronic intractable IBD that can invade the entire gastrointestinal (GI) tract from the mouth to the anus, with major symptoms such as abdominal pain, weight loss, diarrhea, and bloody stools. It usually occurs in young people in their teens and 20s. In addition, complications requiring surgical treatment such as strictures or perforations of the intestine are common. The pathomechanism of CD also involves a combination of genetic and various environmental factors [4–7]. It is mainly reported in Western developed countries [13]. Although it is a rare disease in the East, the incidence of CD has continued to increase recently in epidemiological studies in Japan, South Korea, and other Asian countries [19, 20]. Endoscopic findings of CD are characterized by irregular, asymmetrical, and discontinuous (skipped) inflammatory lesions (Fig. 19.2). An inflammation invading the digestive tract other than the colon suggests CD. In mild to moderate cases, partial hyperemic changes and mucosal friability are observed along with loss of normal mucosal vascular patterns. In advanced diseases, characteristic cobblestone appearances and ulcerative lesions are observed. Because it often invades the terminal ileum (Fig. 19.2a), tissue biopsy at this site plays an important role in its diagnosis. The rectum is often preserved, which is a point to distinguish CD from UC. Unlike UC in histology, inflammation is observed throughout the whole layer of intestine in CD (Fig. 19.2d).

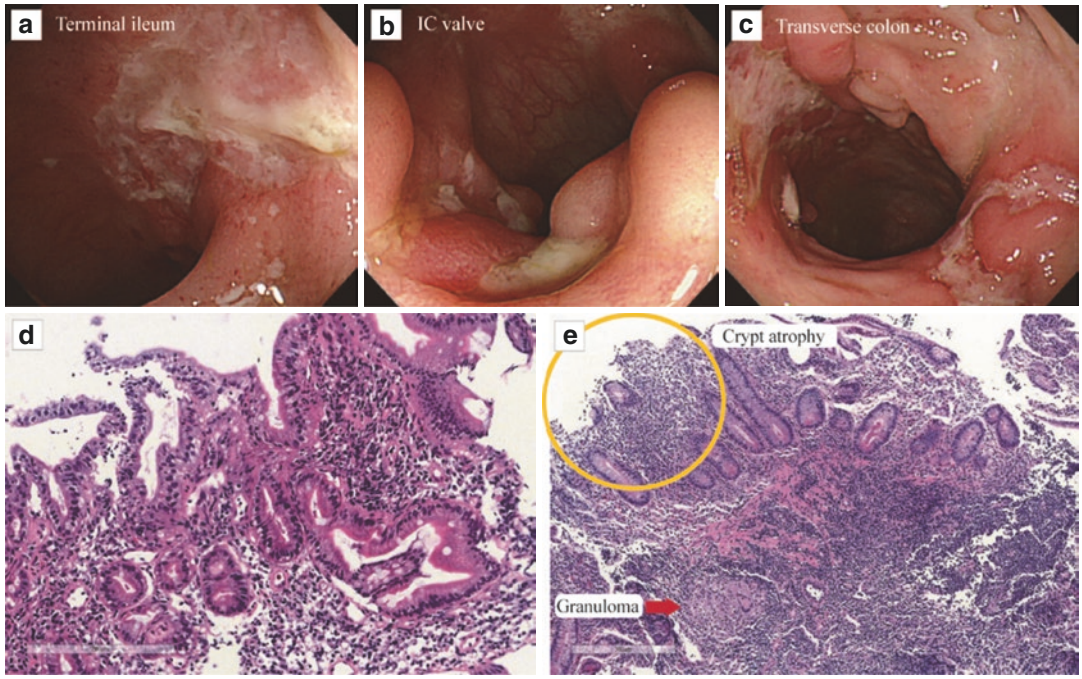

Fig. 19.2 Endoscopic and histologic features of Crohn's disease. (**a**–**c**) Irregular, deep ulcers along with edematous, hyperemic change of the mucosa and characteristic cobblestone appearances are observed in the terminal ileum, ileocecal valve, and transverse colon, respectively. (**d** and **e**) Histologically, inflammation invades the whole layer, with characteristic non-necrotic, noncaseating granulomas observed which are not seen in ulcerative colitis

The presence of a granuloma without central necrosis or caseous change (in about 15–70% of cases) is also a pathognomonic finding of CD [21]. If the upper GI tract or small intestine is suspected of invasion, diagnosis can be obtained through esophagogastroscopy or capsule endoscopy, although capsule endoscopy is contraindicated in cases with suspected stenosis. Crohn's disease activity index (CDAI) is mainly used for assessing severity of the disease [22], which comprehensively evaluates patient symptoms and endoscopic findings.

19.3 Epidemiology and Incidence of Inflammatory Bowel Diseases

As with other inflammatory diseases, differences between males and females are also observed in IBDs. Several studies have shown that adult CD tends to occur more in females. This trend has been observed in Western cohort studies, although it has not been apparent in Asian cohort studies [23–27]. Conversely, most studies on UC have reported that UC is more common in males [28–31]. The incidence of CD is more common in males in children. This pattern reverses at around puberty, with CD occurring more in females in adulthood [27, 28, 32–37] (Fig. 19.3).

In recent studies on the occurrence of IBD, the predominance of CD in females is significant compared to that of UC in males. In a Canadian study of age-specific incidence and prevalence of IBD, reported occurrence rates of CD and UC in females compared to those in males are 1.31 and 1.02, respectively [28]. A Danish cohort study has reported that occurrence rates of CD and UC in females compared to those in males are 1.35 and 1.08, respectively [38]. Meanwhile, meta-analysis studies published in China have reported that both CD and UC are more common in men [39, 40], suggesting that the occurrence of IBD might be affected by regional and environmental factors. There might be differences in the severity of the group of patients included in the analysis

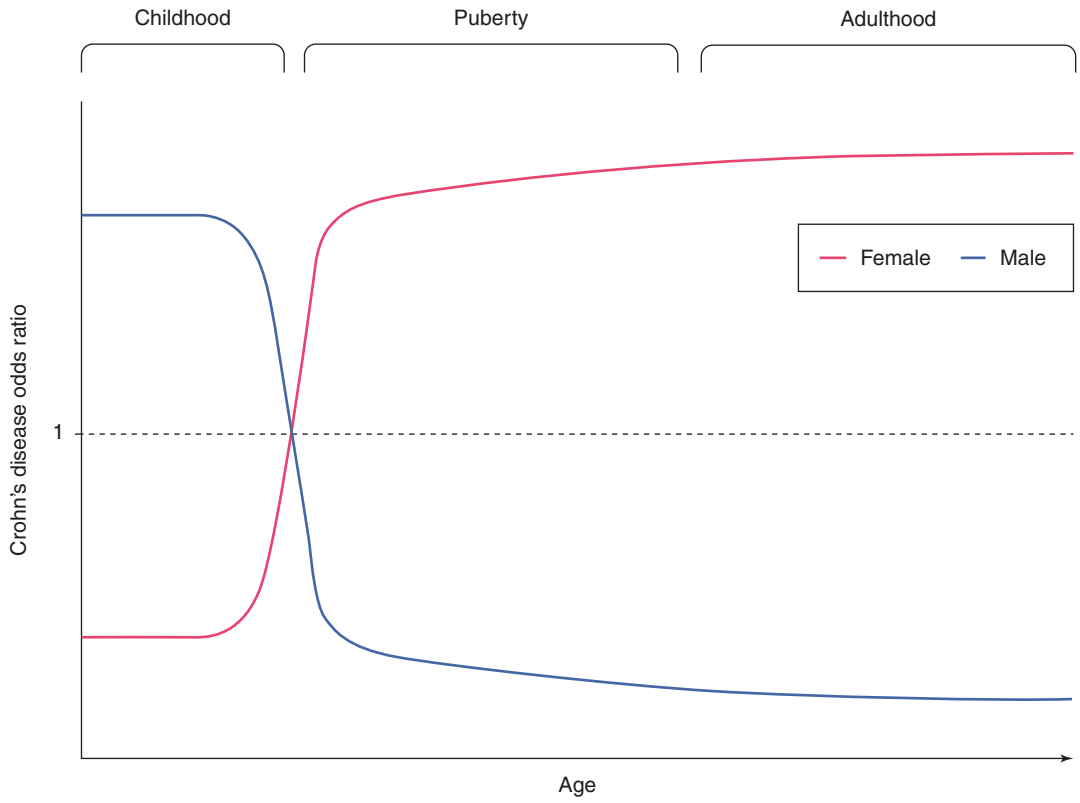

Fig. 19.3 Differences in the risk of developing Crohn's disease by age and gender in the life cycle. Males show a higher risk of Crohn's disease than females during childhood. This trend reverses around puberty with hormonal changes. The risk of Crohn's disease in females increases gradually, which is higher in females than in males during adulthood (adapted from Goodman et al. [37])

as the severity of the disease is also affected by sex. A study of more than 2300 patients including various races has found that CD is 1.2 times more common in females and UC is 1.3 times more common in males [41]. One study on African American in the United States has shown that the occurrence of CD has a more prominent female predominance [42].

In South Korea, a study of 5600 patients with CD and 10,000 patients with UC from 2011 to 2014 has reported that both CD and UC are more common in males (male-to-female ratio: 2.4 in CD and 1.5 in UC) [43]. A recent locoregional study of Songpa-Gangdong district residents in South Korea has also reported higher incidence of CD and UC in males than in females [44]. These results are different from Western studies reported to date. Due to limitations of retrospective data analysis and limited area study in each case, large-scale studies focusing on sex differences in the incidence and prevalence of IBDs are needed in the future.

19.4 Symptoms and Complications of Inflammatory Bowel Diseases

IBDs show a variety of clinical manifestations, making it difficult to distinguish them from other intestinal diseases such as irritable bowel syndrome and infectious enteritis [45]. Thus, medical history of patients should be taken closely. Abdominal pain and diarrhea are common in both CD and UC. However, bloody stools are more common in UC (83–95%) than in CD (40%) [46], whereas weight loss and perianal diseases are more frequent in CD than in UC. About 17% of IBD patients are known to have extra-

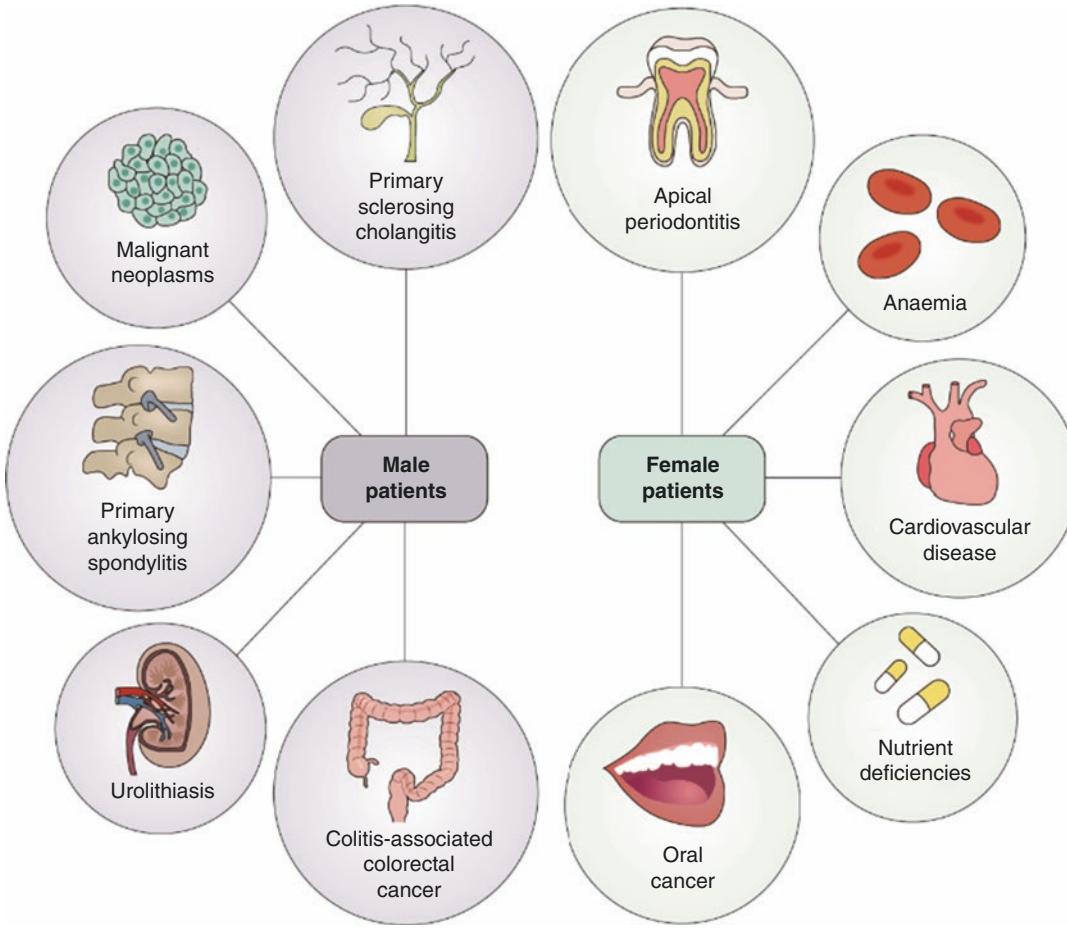

Fig. 19.4 Sex differences in extra-intestinal manifestations of inflammatory bowel disease. Extra-intestinal complications of inflammatory bowel disease differ between males and females, with males having higher risks of malignancies including colitis-associated colorectal cancers, primary sclerosing cholangitis, urinary tract stones, and ankylosing spondylitis (left) and females having higher risks of cardiovascular complications, anemia, malnutrition, periodontitis, and oropharyngeal cancers (right) (adapted from Goodman et al. [37])

intestinal symptoms [47]. These sex-specific disease severity differences vary from study to study. Being males has been reported to be a risk factor for severe diseases in several studies [48]. On the other hand, a higher remission rate in males and a higher disease activity in females have been reported in others [49, 50]. There was also a study reported that there was no significant sex difference [51].

Results so far show that females with CD and males with UC are more likely to be accompanied by extra-intestinal manifestations and sex differences in these extra-intestinal involvements are also observed [37] (Fig. 19.4). The most commonly invaded organs include the skin, joints, eyes, and liver. Approximately 25–40% of IBD patients have complications such as peripheral arthritis, erythema nodosum, primary sclerosing cholangitis, and episcleritis [52, 53]. Rheumatoid symptoms and iron deficiency anemia have been found to be more common in female patients [54–57], although these studies were conducted in limited areas or in small numbers of subjects.

The most serious complication of IBD is malignancy, including sporadic and colitis-associated colorectal cancer. The risk of colorectal cancer is higher in male patients than in female patients [58, 59]. The wider the range, the worse

the degree of inflammation, and the higher the risk [60, 61]. The cancer risk is higher if primary sclerosing cholangitis or family history of colorectal cancer coexists with IBD [60, 61]. Studies in North America and Europe have reported that patients with IBD have 1.1 to 2.2 times higher risk of developing colorectal cancer than normal controls [62–65]. A population-based study using the Utah Cancer Registry has revealed that patients with IBD develop colorectal cancer at an early age than the control group, with male patients having a higher risk of colorectal cancer [66]. Other European studies have also reported a significant increase in cancer incidence in male patients with UC [67]. The risk of bowel resection associated with cancer and antibiotic-resistant pouchitis has been reported to be higher in male patients than in female patients [68]. The risk of death from lymphatic or hematopoietic malignancy is also higher in males than in females [69]. Other than colorectal cancer, the risk of adenocarcinoma, lymphoma, and neuroendocrine tumors in the small intestine also seems to rise in patients with IBD [70], especially in patients with ileal-invading CD [71], although there is no analysis of sex-specific differences yet. Primary sclerosing cholangitis is one of the most common pancreatobiliary complications of IBD. It has been reported to be associated with significantly lower survival rates and increased risk of developing bile duct cancer and requiring liver transplantation [72]. Among them, the risk of liver transplantation, cancer, and death in female patients is known to be lower in females than in males [73].

In males with IBD, the risk of ankylosing spondylitis and urinary stones is increased [37, 74, 75]. The risk of urinary tract cancer associated with the use of thiopurine is also increased [76]. In CD, the risk of stroke is also increased, with a study reporting a higher risk of stroke in females than in males [77]. There are also reports of elevated risk of periodontitis and oral cavity cancer in female IBD patients [78, 79]. Deficiencies in trace elements such as vitamin D, zinc, and selenium are more frequent in female patients [80]. One report has suggested that these deficiencies might be linked to cardiovascular complications such as thromboembolism and arrhythmia [81]. As such, sex differences are observed in symptoms, severity, and extra-intestinal complications of IBD. However, there have been few well-designed, large-scale studies. Thus, further research is needed.

19.5 Pathophysiology of Inflammatory Bowel Diseases

Pathophysiology of IBD is very complex, making it difficult to be explained by one factor. However, most studies have suggested that the pathophysiology of IBD is associated with the immune system of intestinal mucosa, with dysregulations of innate and acquired immune responses being important mechanisms. Recently, it has been shown that female hormones such as estrogen, progesterone, and luteinizing hormone (LH) can affect various GI activities, including GI contraction, GI emptying, and sensitivity to pain [82, 83]. Thus, female hormones might affect the development of IBD and the activity of the disease. Furthermore, gut microbiomes play a role in modulating the immune system of intestinal mucosa, with sex hormones having effects on gut microbiomes. Here, the pathophysiology of IBD will be described in terms of sex difference.

19.5.1 Hormonal Factors

Estrogen affects the expression of adherent proteins in the mucosal barrier that protects the host from pathogens. After administration of 17β-estradiol to azoxymethane/dextran sulfate sodium (AOM/DSS) colitis mouse models, increased expression levels of mucin 2 (MUC2), zonula occludens 1 (ZO-1), occludin (OCLN), and claudin 4 (CLDN4) genes and decreased colorectal permeability are observed, while expression levels of genes and protein related to inflammation such as Krüppel-like factor 4 (KLF4), nuclear factor κB (NF-κB), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) are observed to be decreased [84]. Similar results have been observed in human. When 17β-estradiol is given to CCD841CoN, a

normal female colon epithelial cell line, the inflammation is decreased as NF-κB and COX-2 expression levels are reduced, while heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1) expression levels are increased [85]. Depending on the expression and activity of estrogen receptors, changes in intestinal microenvironment and mucosal barrier functions appear to result in different inflammatory reactions in male and female IBD patients.

Meanwhile, there are reports of the correlation between oral contraceptive use and risk of IBD. A meta-analysis conducted in 2008 has compared the risk of IBD in females with and without using oral contraceptives and found that the risk of CD (relative risk (RR) 1.46; 95% confidence interval (CI), 1.26–1.70; $p < 0.001$) and UC (RR 1.28; 95% CI, 1.06–1.54; $p = 0.011$) occurrence are both higher in females using oral contraceptives [86]. A large-scale meta-analysis conducted in 2017 has also shown a 24% higher risk of CD and a 30% higher risk of UC in females exposed to oral contraceptives [87]. Another prospective study of more than 200,000 subjects has reported a higher risk of CD in females using oral contraceptives, with RR of 2.82 [88]. Similarly, a study in Denmark has shown an increased risk of developing IBD in females with endometriosis than in healthy controls (standardized incidence ratio: 1.5, 95% CI, 1.4–1.7), suggesting that increased estrogen secretion is a potential risk factor for the development of IBD [71]. Increased estrogen level and disease severity of IBD also seem to be correlated, with studies reporting symptoms of IBD such as diarrhea worsening just before menstruation [89], menstrual cycle irregularities preceding the diagnosis of IBD [90], and irritable bowel symptoms increased in healthy females before menstruation [91, 92]. In addition to the role of estrogen in modulating inflammation and immune system, estrogen also contributes to thrombogenesis [93]. To understand why estrogen is a risk factor for IBD in situations such as oral contraceptive use and endometriosis, it has been explained that estrogen might activate coagulation cascades and lead to multiple infarction which in turn can facilitate the progress of IBD [85].

In terms of dysplasia and cancer development, sex hormones and their receptors might promote or downregulate the carcinogenesis pathway. It is well known that IBD is associated with an increased risk of colorectal cancer, which is related to long-standing chronic inflammation as mentioned above [62–65, 94]. Some studies have demonstrated effects of sex hormones on carcinogenesis in IBD patients. For example, Principi et al. have reported the influence of estrogen receptor (ER) α/β balance and concluded that ERβ appears to parallel apoptosis, thus exerting an anti-carcinogenic effect [95, 96]. They have suggested that phytoestrogens could be used as a chemopreventive agent for colorectal cancer even when the disease is the long-term consequence of chronic inflammation [96]. Cancer surveillance and prevention are important for patients with IBD. Further investigations on this topic are needed.

19.5.2 Immune Mechanisms

Studies have been conducted on the pathophysiology of IBD associated with the immune system of intestinal mucosa. Dysregulations of innate and acquired immune responses are known to be important mechanisms. Innate immune response is the first gateway to protect an object from exogenous antigens, a non-specific immune response that occurs within minutes to hours. This process is initiated by receptors such as toll-like receptors (TLRs) on the cell surface and nucleotide-binding oligomerization domain (NOD)-like receptors in the cytoplasm [97]. It is modulated by various cells including epithelial cells, neutrophils, dendritic cells, monocytes, macrophages, and natural killer cells [98]. Recent studies have shown changes in expression levels of these receptors and activities of these regulatory cells in patients with IBD. For example, aggregation of neutrophils in response to mucosal damage can decrease the production of interleukin (IL)-1β and IL-8 [99]. Reduced response to lipid polysaccharides in mucosa with NOD2 gene variation [100] and deactivation of NF-κB [101] have been observed in CD patients. These

may lead to decreased protective function of mucosa and invasion of pathogenic microorganisms, contributing to the development of IBD [102]. Other studies have also explained that failure of NOD2 to contribute to immune tolerance can lead to the lack of inhibition of TLR2 stimuli, leading to activation of inflammatory reactions and excessive Th1 response triggers [103, 104].

IL-23 is a cytokine that plays an important role in early reactions in both innate and acquired immune responses. IL-23 receptor polymorphisms are known to be associated with both CD and UC, suggesting that IL-23 might represent a common inflammatory molecule in IBD. Recent studies have also shown that IL-23 can act on cells in the innate immune system and induce Th17 cytokine production by innate lymphoid cells (ILCs) that share phenotypes of lymphoid tissue inducer (LTi) cells [105]. CD is also associated with *ATG16L1* and *IRGM* gene variations involved in autophagy. *ATG16L1* coding mutation T300A is associated with an increased risk of CD [106–108]. Autophagy is very important for host defense against microorganisms in cells. In patients with NOD2 or *Atg16L1* mutations, the process of autophagy is inhibited which can contribute to the development of IBD [109]. In addition, deficiencies in epithelial barriers and increased intestinal permeability have been observed in patients with IBD [110]. The first physiological barrier to antigens is the mucus layer covering the intestinal epithelium [111], and the second barrier is the epithelium consisting of epithelial cells such as enterocytes, goblet cells, and Paneth cells. In addition to the formation of physical barriers to bacteria, epithelial cells also have a function of secreting antibacterial peptides. Defects in antibacterial peptide production function of epithelial cells have been observed in patients with CD [112].

Unlike innate immune responses, adaptive immune response is highly specific. It often takes days, depending on the type and number of T cells. Th1 cells induced by IL-12 can produce large amounts of IFN-α, while Th2 cells can produce IL-4, IL-5, and IL-13 [113]. Abnormal Th1 immune responses are thought to cause intestinal inflammation in CD, with mucosal T cells of CD patients producing more IL-2 and IFN-γ than those of UC patients or normal controls [114]. Meanwhile, abnormal NK T cells in UC can produce more IL-13, a Th2 cytokine, than those in CD patients or normal controls [115, 116]. Based on these, there are views that CD is Th1 immune response dominant and UC is Th2 immune response dominant [117]. However, conflicting results have also been reported. For example, one study has shown a similar increase of IFN-γ in tissues of both CD and UC patients [118]. Others have reported a decrease of IL-13 in intestinal mucosa of UC patients compared to that of CD patients and normal controls or no significant differences in IL-13 and IFN-γ concentrations between CD or UC and normal control groups using in vitro incubation of intestinal mucosal biopsy samples [119, 120]. To sum this up, the concept of describing IBD as Th1/Th2 immune response alone remains controversial.

Th17 is a T cell that produces large amounts of IL-17A, IL-17F, IL-21, and IL-22. It is derived by the combination of IL-6 and transforming growth factor (TGF)-α facilitated by IL-23 [121]. Inflammatory actions of Th17 cells and their product, cytokine IL-17A, have been widely studied. Many studies have observed increased levels of IL-17A in mucosa of patients with CD and UC than in normal intestinal mucosa [114, 122, 123]. In addition, Th17 cell is an important source of cytokine IL-21 which is associated with IL-2 that is increased in IBD [124, 125]. It expresses IL-23 receptors on its cell surface. Studies have revealed the role of Th17 in the development of IBD [126]. It is well known that such complex and diverse immune mechanisms are involved in the pathophysiology of IBD, although many areas have not been clearly identified. Induction and modulation of these immune responses vary greatly from individual to individual. Thus, additional research should be con-

ducted, including studies on differences between males and females.

19.5.3 Genetic Factors

Until now, studies of first-degree relatives and twins have shown that there is a genetic predisposition to the development of IBD. The incidence of CD or UC is known to be around 2–15% in relatives of IBD patients [127]. Having patients with IBD among family members is the most definite risk factor for CD and UC [128]. Twin studies have shown higher matching rates in CD than in UC, with similar clinical manifestations between them [129, 130]. On this background, genetic studies using techniques such as genome-wide association study (GWAS) and whole genome sequencing (WGS) have been conducted, and more than 240 related genes have been reported to date [131, 132]. Regarding sex difference in genetic factors, it has been reported that the predominance of IBD in women is noticeable in cases with a family history of IBD [133]. That study has also found that the probability of heredity from women to women is higher than that from men to women [133]. This phenomenon is referred to as female imprinting, which is thought to be particularly prominent in CD. Sex-specific genetic variants known to be associated with IBD include R30Q DLG5 (increases risk of CD in males), IL-23R mutation L310P (having protective effect against UC in females), and single nucleotide polymorphism in IL-10 promoter sites (increases risk of UC in females) [134–137]. However, the exact mechanisms for these effects remain unclear, requiring further research. Studies have shown that X chromosome aberrations play an important role in the development of autoimmune diseases and that X chromosome deficiency in peripheral T and B lymphocytes is associated with the production of autoantibodies, leading to the development of various autoimmune diseases including primary biliary cirrhosis, autoimmune thyroid disease, Raynaud's syndrome, and systemic sclerosis [138–140]. Research related to this is expected to be significant in the future.

19.5.4 Changes in Gut Microbiota

Gut microbiomes play a role in modulating the immune system of intestinal mucosa. After administrating sex hormones to animals, studies have shown that gut microbiomes play an important role in immune response, especially early in life [141, 142]. Sex-specific difference in gut microbiome has been found to be one major pathophysiology in many diseases including IBD [143] because gut microbiome is involved in the development of IBD as an immune modulator [144]. In a study using an IBD mouse model, changes in gut microbiomes are observed [92, 145]. Such changes are more significant after oophorectomy [146, 147]. In a male enteritis mouse model, estrogen shows immune-protective effects through regulatory T (Treg) cell expansion, which is proportional to the expression of Erβ. Decreased ERβ expression in female mice can result in decreased Treg cells and increased inflammations of the small and large intestine [37, 143] (Fig. 19.5). Decreased ERα expression in male mice can increase intestinal inflammation, while the opposite is seen in female mice. Thus, ERβ expression is thought to have a protective effect on enteritis [143]. In addition, one study of fecal microbiomes in male and female acute enteritis animal models derived from 2,4,6-trinitrobenzenesulfonic acid (TNBS) has shown more severe inflammation in males than in females of both wild-type and tumor necrosis factor (TNF) −/− mutant mice in an age-dependent manner [148]. Meanwhile, analysis of fecal microbiomes of C57BL/6 mouse has shown a difference in β-diversity between males and females, although such difference is eliminated in IL-10 deficiency (knockout, KO) mice inflammatory models with increased *Firmicutes*/*Bacteroidetes* ratio [145]. In addition, in female mice, *Proteobacteria* are increased in IL-10 KO mice than in wild-type mice, suggest-

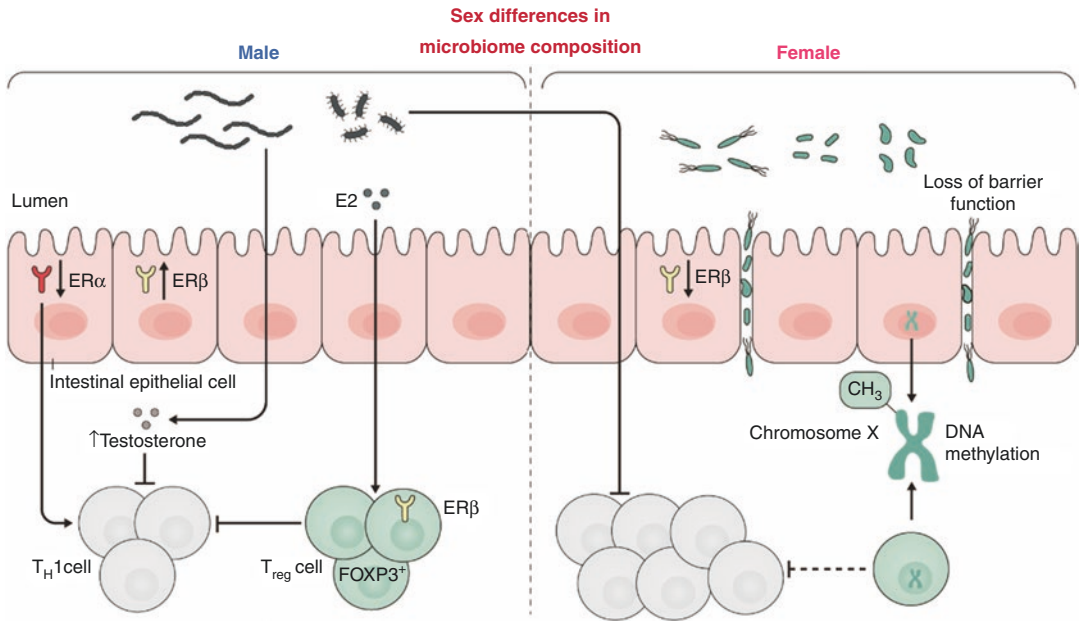

Fig. 19.5 A schematic diagram of mechanisms of sex-based differences in intestinal microbiota in the development of inflammatory bowel disease. Microbiota might contribute to sex-based differences in IBD by several different mechanisms, including differences in commensal composition between male mice and female mice, the ability of the microbiota in male mice to induce testosterone that has protective effects, and the induced protection in female mice after fecal transplantation from male donors. Estrogen (E2) has also been shown to have immunoprotective effects during experimental colitis by inducing regulatory T (Treg) cell expansion and function in male mice in an estrogen receptor (ER)β-dependent manner. In addition, decreased ERβ has been observed in both epithelial and Treg cells from female mice that are prone to ileitis and/or colitis. It can promote intestinal epithelial barrier dysfunction and worsening of disease. Decreased expression of ERα in male mice can result in the exacerbation of intestinal inflammation, but has an opposite effect in female mice, suggesting that skewing toward ERβ signaling can induce global protection from colitis. Finally, differential transcription (e.g., by DNA methylation) of genes located on chromosome X can regulate molecules that affect downstream sex-based differences in the pathogenesis of IBD. *T_H1 cell* T helper 1 cell (adapted from Goodman et al. [37])

ing that gut microbiome has a significant immune-modulating effect [145]. Based on changes in gut microbiomes of animal IBD models, there are significant sex-dependent differences in changes of gut microbiomes associated with immune responses, suggesting sex differences in the occurrence of IBD.

19.5.5 Environmental Factors

Exposure to different environments has also been suggested as one of the reasons for the difference between males and females in the development of IBD [149]. Studies so far have reported that appendectomy and smoking can increase the risk of developing CD in females [150–152]. Smoking is a well-known risk factor for CD. The smoking rate in males was much higher than that in females at all ages in the past. However, in recent years, the smoking rate in young women has gradually increased [153]. Previous studies have shown that middle-aged female CD group has the highest smoking rate among patients with IBD [153]. Another study on IBD patients has reported that the smoking rate in females is higher than that in males [154]. In the past, smoking was thought to be a protective factor against UC, but a risk factor in CD [152]. However, recent studies have reported that smoking and IBD have a more complex relationship than the past concepts, showing sex-specific differences. Cosnes et al. [155] have concluded that smoking has a protective effect against the occurrence and progression of disease

and that it can reduce the need for immunosuppressive treatment in male UC patients but not in females. They also reported that smoking had a detrimental effect in female CD patients but not in males [155]. Given these current results, active recommendation of quitting smoking in females with IBD is believed to bring benefits to treatment for both UC and CD [156].

Many other environmental factors (including drugs, occupational chemicals, sunlight, and vitamin D) and lifestyle factors (including sleep and shifts) can potentially contribute to the development of IBD and disease complications, with significant differences in risk exposure between males and females [156]. Sex-related differences have been observed after the use of antibiotics, with IBD being especially higher in young males after antibiotic treatment [157]. However, appendectomy is associated with increased risk of CD in females [151]. Although these sex differences are thought to be associated with sex-specific differences in gut microbiomes [158, 159], the specific mechanism remains unclear. Further research is needed on the specific effects of these environmental factors on IBD in each sex in the future.

19.5.6 Dietary Factors

Compared to traditional Mediterranean and Asian diets, Western-style diets usually contain more refined carbohydrates, saturated fats, red meat, dairy products, and processed foods with fewer vegetables, fruits, beans, whole grains, raw foods, and fiber. In addition, Western-style diets have high calories from saturated fats, glucides, and animal proteins. So far, studies have been conducted on the relevance of Western diets to obesity, hypertension, chronic nephropathy, and many non-communicable diseases [160–162]. It has been found that these dietary habits can promote inflammatory reactions in the GI tract through a variety of mechanisms, including gut microbiological changes [163–166]. Western-style diets can affect immune responses, intestinal microbiomes, and mucosal barriers [167]. They also contain lower levels of anti-inflammatory and antioxidant nutrients. Thus, diet Westernization affects the prevalence of IBD. A recent study on African children has shown that changes in rural vegetarian diets to Western diets (an increase in intake of animal protein, saturated fat, and processed refined foods) have resulted in dramatic changes of intestinal microorganisms and intestinal functions [168]. In addition, the decrease in fiber intake has reduced microorganisms for fermenting dietary fibers [168]. Furthermore, numbers of bacterial groups that could metabolize animal proteins, fats, and sugars are increased [168]. Even in East Asia, which has traditionally shown a low prevalence of IBD, the prevalence seems to be increasing due to diet Westernization [168].

Although it is difficult to determine the exact role of diet in the development of IBD, given that the incidence of IBD increases as industrialization and Westernization progress, it is certain that diet can affect the occurrence of IBD and control the activity of the disease. Although there are many different types of food without definitive guidelines for diet currently, dietary control can help treat IBD, maintain remission, and improve patients' quality of life [164]. It seems necessary to draw up guidelines on diet and nutrition in patients with IBD through research including sex and individual differences in the future.

19.6 Treatment of Inflammatory Bowel Diseases

IBDs are chronic. The goal of IBD treatment is to improve patient's quality of life after inducing remission. Prior to treatment, the range, severity, and clinical aspects of the disease as well as the response to existing treatment, side effects, extra-intestinal manifestations, and disease behavior (especially in CD) should all be considered.

The goal of treating UC is to improve symptoms and mucosal inflammation, induce remission, and maintain it for as long as possible to improve patient's quality of life. Based on the intruded area of inflammation, the severity of UC can be classified as proctitis (inflammation invades up to 15 cm from anal verge), left-sided colitis (inflammation invades up to splenic flex-

ure), and extensive colitis (inflammation invades whole colon) [169]. In UC proctitis, topical 5-aminosalicylic acid (5-ASA) drugs can be attempted initially. Oral 5-ASA treatment is recommended for remission induction in patients with left-sided and extensive colitis with mild to moderate activity. Systemic steroid treatment is required when a patient's symptoms deteriorate or remain with sufficient dose (over 2.4 g/day) of 5-ASA treatment for more than 4 weeks. In addition, worsening symptoms in patients undergoing azathioprine (AZA) maintenance therapy will need oral steroids. Treatment with biologics such as anti-TNF agents is recommended when sufficient dose and duration of steroids or steroids and thiopurine coalescing administration are inefficient or when the patient is intolerable to maintenance therapy [169].

In addition to inducing and maintaining remission of active stage disease, preventing complications by inhibiting the progression of the disease is also emerging as an important treatment goal in CD. When the patient is considered to be an active stage of CD, possibilities of intestinal infections, abscesses, fibrosis and stenosis, bacterial overgrowth, bile absorption disorder, gallstones, and GI motility disorders should be excluded as possible aggravating factors. Sulfasalazines can be used for induction of disease remission in mild CD patients. In addition, 5-ASAs can be considered for mild cases with fewer drug side effects and convenience of administration, although its remission-inducing effect is limited. Topical steroid administration is preferred for induction of disease remission for mild to moderate CD, which is confined to the terminal ileum. Systemic steroids should be considered for cases with low response to 5-ASA or topical steroids. If there is no improvement in systemic steroid treatment or if steroids cannot be discontinued, biologics such as anti-TNF agents can be attempted. In addition, in CD, surgical treatment should be considered as an option if it does not respond to adequate medical treatment. The treatment plan needs to be determined through sufficient interactions between gastroenterologists, surgeons, and patients [170].

Looking at sex-specific considerations in the treatment of IBD reported so far, first, male patients with IBD are more likely to receive systemic treatment than female patients [171, 172], which might be associated with high accessibility to medical care in males. However, in a study of 55 patients with infliximab, males have been reported to be less attractive to treatment than female patients [173]. A study of 317 CD patients with infliximab has reported higher remission rate in male patients, while males show significant lower incidence of vascular complications such as ischemic heart disease and peripheral vascular disease compared to females [174]. Sex differences in steroid and vedolizumab treatment have also been reported, with fewer requirement of steroid treatment in males [175] and higher rates of drug cessation due to hypersensitivity during vedolizumab treatment in females [176]. The difference in responses to anti-TNF drugs between males and females is thought to be attributable to genetic influences. In the analysis of factors affecting blood drug concentrations of infliximab and adalimumab, factors that can lower blood drug concentrations are males and polymorphism (variable number of tandem repeat (VNTR)) of Fc fracture of IgG receptor and transporter gene (FCGRT) [177]. These findings suggest that responses to biological drugs may vary due to sex-specific genetic differences. Thus, consideration of genetic differences between males and females is essential as biologics are thought to be the mainstay of future IBD treatment.

19.7 Conclusions

The number of patients with IBD and the burden of disease are increasing. Although there are many IBD treatment methods due to the development of new drugs, there are still many challenges. Sex differences have been identified in the occurrence and progress, symptoms and complications, reactions to treatment, and adverse drug reactions of IBD. As mentioned above, CD occurs more in males during childhood, but this tendency is reversed around puberty, resulting in

more cases in females during adulthood, while UC occurs more in males. In addition, females with CD and males with UC are more likely to exhibit extra-intestinal manifestations. Especially, male UC patients have a higher risk of colon cancer. Estrogen plays a major role in the underlying sex differences, which contribute to the development of IBD through immune modulation, thrombosis formation, and intestinal microbiological changes that can also increase the incidence of IBD in situations where estrogen secretion increases. However, research on sex differences in IBD is still insufficient so far. Thus, an analysis, especially on people, will be needed. In the past, the sex of patients was not considered in the diagnosis or treatment of IBD. However, it should be considered from now on since males are less compliant with drugs and biological drugs have more side effects in females, making it the first step in providing personalized and tailored therapy.

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Sex Difference of Colorectal Cancer

20

Nayoung Kim

20.1 Introduction

Colorectal cancer (CRC) is a significant cause of morbidity and mortality in the world. For example, CRC was the third most common cancer globally in 2012 and the incidence is expected to reach 2.2 million by 2030 [1, 2]. CRC occurs at a higher frequency in men than in women [3]. When describing sex differences in CRC, it is important to discriminate between sexual dimorphism (biological differences in hormones and genes) and gender differences (non-biological differences in societal attitudes and behavior) [4]. The incidence and mortality of CRC in populations over 65 years old are higher in women than those in men implying that CRC is a major health threat among older women [5, 6]. Considering the longer life expectancy of women compared to that of men, gender-targeted strategies to prevent and treat CRC should be properly delivered to improve the quality of life, especially, in older women [5]. Usually CRC is classified as right-sided (proximal) and left-sided (distal) colon cancer. Right colon cancer was known to be more aggressive type tumor compared to colon cancer [5], and the percentage of patients with proximal colon cancer is often higher in women than in men [7]. In addition, the pathophysiology of CRC such as chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) is somewhat different between proximal colon cancer and distal colon cancer [8]. Therefore, in this paper, we reviewed the sexual dimorphism (biological differences in hormones and genes) and gender differences (non-biological differences in societal attitudes and behavior) to provide strategies for gender-targeted CRC screening, treatment, and prevention including diet.

20.2 Incidence and Mortality Rate of Colorectal Cancer in the World

The Global Cancer Observatory 2019 shows that the incidence and survival patterns for CRC vary markedly across the world [9]. However, the incidence of CRC in men is consistently higher than in women, and the age-standardized incidence rates (ASIRs) per 100,000 of CRC in the world were 23.6 and 16.3 in the men and women, respectively [9] (Fig. 20.1). Highest incidence is seen in Australia and New Zealand (41.7 and 32.1 in the men and women, respectively), Europe, Eastern Asia, and North America; and the lowest incidence in the South-Eastern Asia, Africa, and South-Central Asia (6.1 and 3.8 in the men and women, respectively) [9] (Fig. 20.1).

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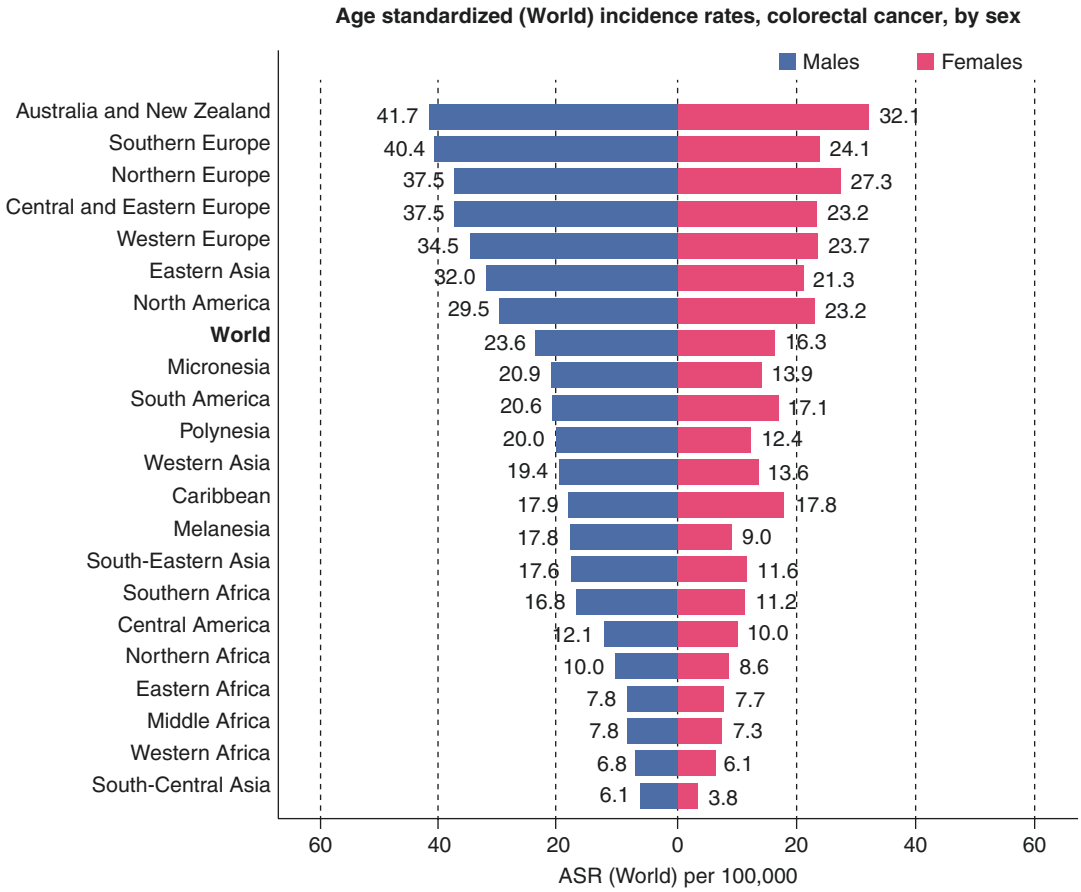

Fig. 20.1 Age-standardized incidence rates of colorectal cancer depending on sex. The incidence rate for CRC varies markedly across the world (Data from International Agency for Research on Cancer (IARC) [9])

Mortality rates from CRC are also higher in men than women, and this is consistently seen across different regions of the world [4] (Fig. 20.2). The age-standardized mortality rate for men is 50% higher (10.8 per 100,000 person-year) than for women (7.2 per 100,000 person-year) [9]. It is challenging to determine how much of the sexual dimorphism in CRC mortality is attributable to the sex differences in CRC incidence rates [4].

20.2.1 Sex Difference of Incidence of Colorectal Cancer

It is well known that CRC occurs at a higher frequency in men than in women. According to the Global Cancer Observatory [9], the ASIR per 100,000 in men is 45% higher (23.6 per 100,000 person-year) than women (16.3 per 100,000 person-year). Also, men have a 50% higher cumulative risk (CR) to develop CRC than women (CR 2.75 vs. 1.83) [4]. Cancer statistics in Korea also showed that ASIR per 100,000 for incidence in men in 2017 was 30.8 per 100,000 persons, and it was 39.9 in men higher than 23.0 in women [3]. Looking at different age-frames, CRC incidence rates under 50 years old are very low and there is not a clear sex disparity. That is, the ASIR of CRC by age began to show that men have higher incidence rates than women from 45 to 50 years of age in the United States (Fig. 20.3a), the United Kingdom (Fig. 20.3b), and China (Fig. 20.3c) [4]. In every age group above 50, women have lower incidence rates than age-matched males [10]. This

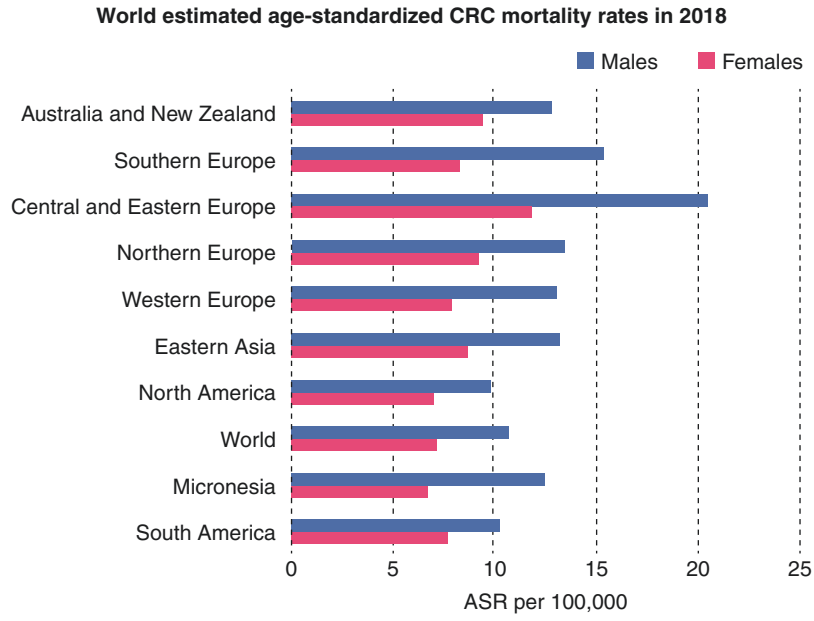

Fig. 20.2 Age-standardized colorectal cancer mortality rates depending on sex (adapted from Abancens et al. [4])

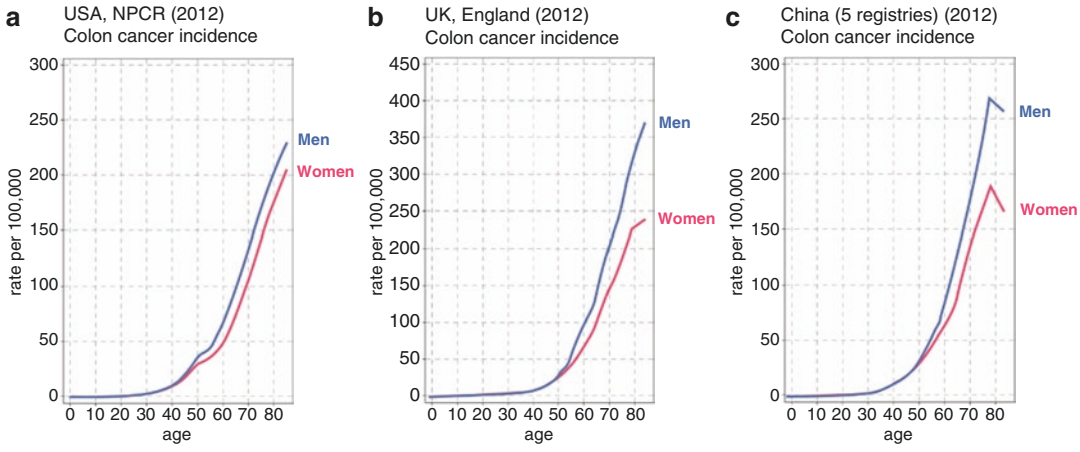

Fig. 20.3 Age-standardized incidence rate of colorectal cancer of men and women in the United States (**a**), the United Kingdom (**b**), and China (**c**). Colon cancer incidence rates by age show men have higher incidence rates than females from 45 to 50 years of age (adapted from Abancens et al. [4])

effectively results in 4–8 years delay in women compared to men, such that women aged 65, for example, have similar CRC incidence to men aged 60 [11]. This difference in CRC incidence between men and women is not a new phenomenon because it has been observed steadily for at least the past 40 years in the United States (Fig. 20.4a), where the incidence was rather higher in the world [12] and for 25 years in Korea where that of CRC was rather lower than the developed countries [13] (Fig. 20.4b). In Korea, the overall cancer incidence rates increased annually by 3.5% from 1999 to 2011 and decreased by 2.7% annually thereafter [3]. Factors such as obesity and smoking evidently contribute to this difference, but a protective role for estrogen in the prevention of CRC has also been proposed in women [14, 15]. Furthermore the incidence of CRC in the postmenopausal women steadily increases, which is very different from that of men

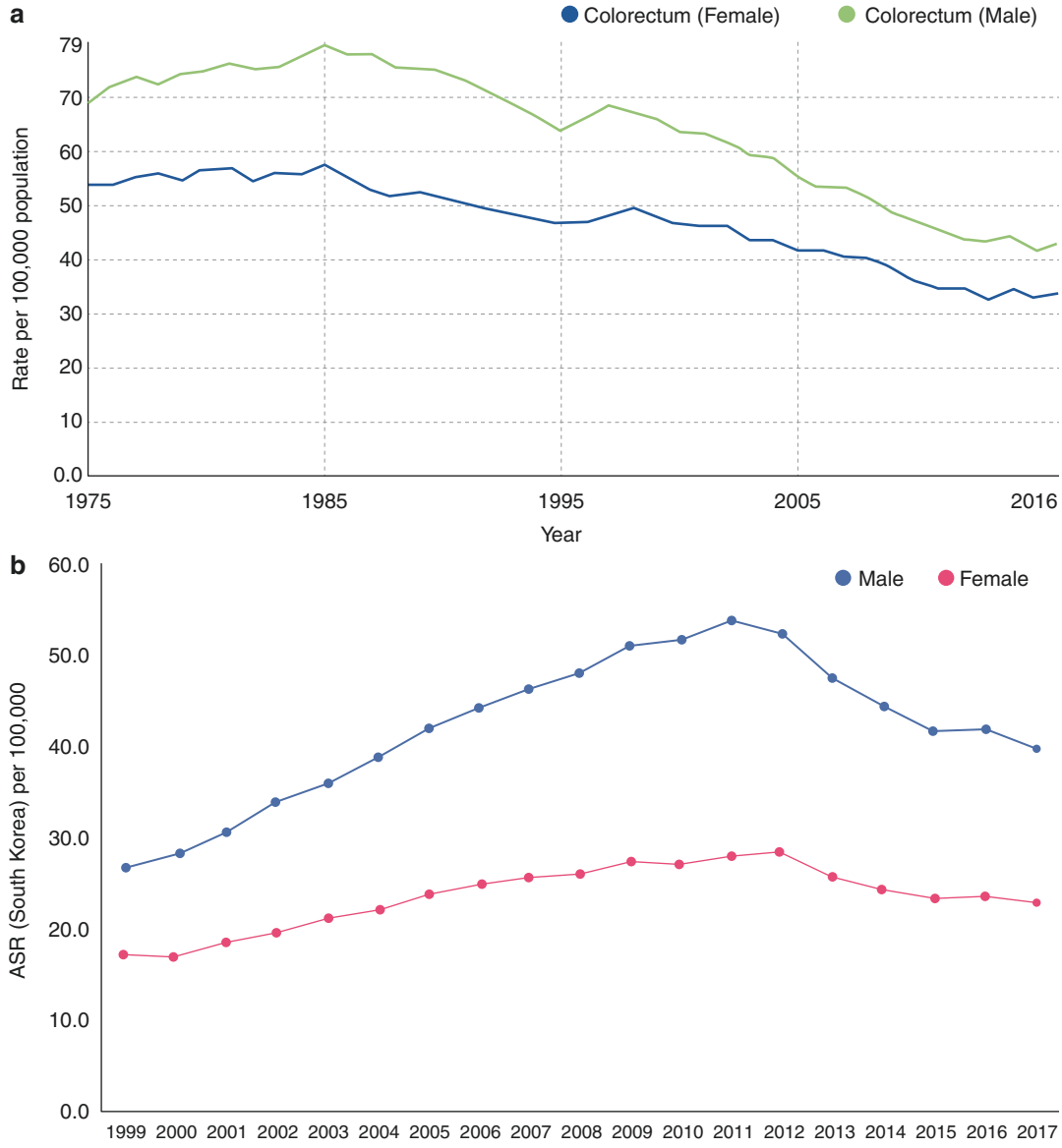

Fig. 20.4 Age-standardized colorectal cancer incidence rates of men and women for past 18–40 years. (**a**) The ASR of colon cancer in men is consistently higher than in women (adapted from SEER 9 registries [12]). (**b**) It was similar in South Korea (adapted from Korea Central Cancer Registry [13])

[3] (Fig. 20.5). This raises the question of whether hormonal status has a direct impact upon incidence or whether hormone abundance influences the contribution of other established risk factors [1]. A number of studies have investigated the gender difference in CRC incidence in the context of different lifestyles and different cultural backgrounds. That is, population-based data collected in the 1970s found that the ASIRs for CRC were similar among men and women [16]. However, within the past few decades, the incidence of CRC in men has increased and exceeded that seen for women, especially in high incidence populations such as in New Zealand, the United States, Canada, Australia, and the United Kingdom [1]. Now this similar trend is observed in the traditionally low-risk populations that are developing a rising incidence, such as Hong Kong, Japan, and

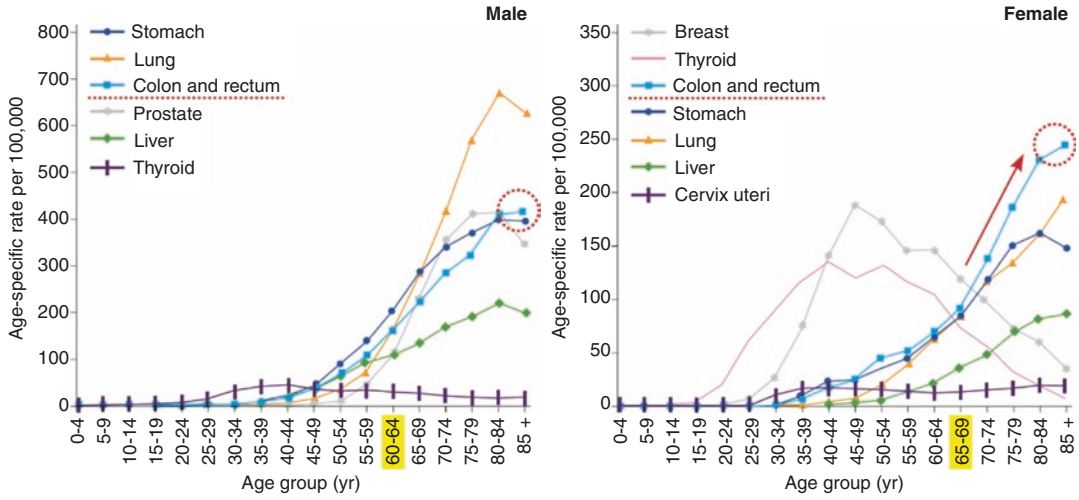

Fig. 20.5 Age-specific incidence rates of colorectal cancer depending on age in the men and women**.** The incidence, survival, and prevalence rates of cancer were evaluated using data from the Korea National Cancer Incidence Database from 1999 to 2017 with follow-up until December 31, 2018 (adapted from Hong et al. [3])

Singapore [1]. This trend is much less apparent in low incidence populations such as in India, Chile, and Thailand [16]. The importance of the environment and lifestyle has been confirmed in migrant studies, where it was revealed that the incidence of CRC in men rises more rapidly than that in women when they immigrate to high from low incidence areas [16]. In contrast to these human studies, azoxymethane/dextran sodium sulfate (AOM/DSS)-induced colon cancer mouse model showed that the CRC incidence was definitely higher in male than female mouse and the treatment of 17β-estradiol during the DSS inflammation period prevented the development of CRC [15]. Our team also reported that endogenous and exogenous testosterone presented a stimulating effect on AOM/DSS-induced colitis and carcinogenicity [17]. Taken together, sex hormones contribute to CRC risk, but this is modulated by lifestyle and environmental factors.

20.2.2 Sex Difference of Mortality of Colorectal Cancer

Mortality rates from CRC are higher in men than women, and this is consistently seen across different regions of the world [4] (Fig. 20.2). For example, a German population-based cohort study including 185,967 patients showed women had significantly better overall (hazard ratio, HR 0.853) and recurrence-free survival (HR 0.857) than men [18]. In the United States [12] (Fig. 20.6a) and in Korea [13] (Fig. 20.6b) were also found similar findings. A meta-analysis from 2017 including 37 clinical trials also showed that women had better overall (HR 0.87) and cancer-specific survival (HR 0.92) than men [19]. In the same way, the EUROCARE-4 study that analyzed data of patients diagnosed between 1995 and 1999 from 23 European countries showed women had a 2.2% advantage in 5-year average and region-adjusted survival for CRC [20]. However, the most recent EUROCARE-5 study, which evaluated patients from 29 European countries diagnosed between 2000 and 2007, did not show the significant advantage for women in CRC survival [21]. In addition, a cross-sectional study from the United Kingdom including 164,980 CRC patients showed no significant age-standardized survival benefit for women compared to men [22]. Generally, the benefit in CRC survival, which has been attributable to sexual dimorphism, has been associated with the premenopause stage in women [4]. That is, premenopausal patients have better 5-year survival rates than age-matched male patients. For instance, younger women (18–44 years) showed

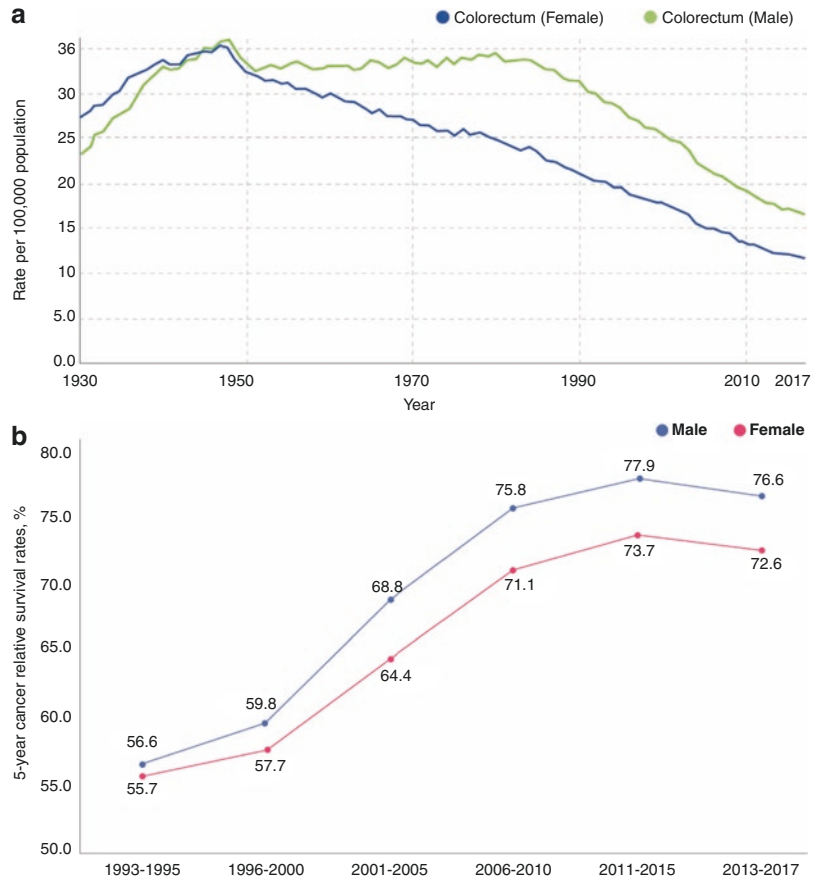

Fig. 20.6 Age-standardized mortality rates of colorectal cancer in men and women for past 18–40 years. (**a**) The age-standardized mortality rates of colon cancer in men were consistently higher than in women (adapted from SEER 9 registries [12]). (**b**) It was similar in South Korea (adapted from Korea Central Cancer Registry [13])

lower mortality compared to older women (over 50 years) [23, 24]. In contrast, CRC women patients over 65 years old showed worse survival rates than age-matched men patients [4]. The reason could be that women patients over 65 years old tend to be diagnosed in a more advanced stage than men and have a more aggressive cancer type [5, 25–27], which is originated from the location and morphology of colon cancer. Actually sex differences exist regarding the type of tumor [4, 5]. That is, women show a higher frequency of right-sided (proximal) tumors than men [5, 28]. Right-sided tumors occur predominantly in women and older patients, and are less common than left-sided (distal) tumors [5]. Patients with right-sided colon cancer exhibited vague symptoms and suffered from more associated diseases and less differentiated compared to left-sided colon cancer [19]. When a Japanese study analyzed a total of 62,350 colon cancer patients, 5-year net survival rates for subjects with left- and right-sided colon cancer were 74.0% (95% confidence interval [CI], 73.4–74.7%) and 70.4% (95% CI, 69.7–71.0%), respectively [29]. Compared with left-sided colon cancers, the excess hazard ratio (HER) for right-sided colon cancers was 1.20 (95% CI, 1.16–1.25) after adjustment for age, sex, and stage [29]. Furthermore, a meta-analysis study reported that patients with right-sided colon cancers had an 18% increase in mortality risk and that this was independent of stage [30]. In addition to the location, right- and left-sided tumors have been shown to differ in several clinicopathological features such as immune infiltration, differentiation, or MSI. High-MSI tumors comprise close to 15% of all CRC cases, and they locate predominantly in the right-sided colon [5, 31]. Differences between right- and left-sided colon cancers are possibly due to differences in genetic

makeup, life style, and/or dietary habits [5]. Chromosomal instability, which is associated with 60–70% of CRC, is more often observed in left-sided colon cancer, and defective genes include adenomatous polyposis coli, Kirstenras, deleted in CRC, and p53 [32–34]. On the other hand, MSI-high, CIMP-high, and BRAF mutation are often observed in right-sided colon cancer [33, 34]. Hereditary non-polyposis CRC is more likely to develop tumors on the right side of the colon, whereas familial adenomatous polyposis is associated with left-sided colon cancer [35, 36]. This MSI status has been shown to impact sensitivity to CRC treatments and prognosis [4]. For example, immunotherapy has been shown to improve prognosis, particularly of MSI-high tumor carrying patients, whereas anti-EGFR and 5-FU adjuvant therapies exert little and no benefit to MSI-H tumors in contrast to MSS tumors [37]. In terms of survival, metastatic CRC patients with right-sided primary tumors have worse survival rates compared to left-sided tumors [38]. In addition, right-sided tumors are more difficult to diagnose by colonoscopy because of their flat shape neoplasia compared to the polyp type neoplasia from left-sided tumors [39] (Fig. 20.7). The decreased gender-specificity of screening tools may therefore explain a higher mortality and shorter 5-year survival rate of women in many regions of the world. Taken together, women have a lower risk to develop CRC than men. Women at a younger age are less likely to die from CRC than age-matched men patients. However, right-sided colon cancer increases which are diagnosed in advanced stage and resistant to chemotherapy resulting in worse prognosis in older women than men.

20.3 Pathophysiology of Colorectal Cancer

CRC develops by sexual dimorphism (biological differences in hormones and genes) and gender differences (non-biological differences in societal attitudes and behavior) [4]. Biological distinction between the sexes is based on the difference in the levels of circulating sex hormones. Especially, 17β-estradiol plays a key role in the prevention of CRC in female. Among gender differences (non-biological differences in societal attitudes and behavior); diet is also very important in the increase of CRC in men. In the case of 17β-estradiol, how it plays a key role in the prevention of CRC has still not been fully discovered.

20.3.1 Sex Hormones

All sex steroid hormones derive from cholesterol and are classified into estrogens (17β-estradiol, estriol, and estrone), androgens (testosterone), and progestogens (progesterone) [4]. Estrogens are synthetized from androgens, which in turn derive from progestogens produced from cholesterol [4]. Sex hormones are produced in the testis (men) and ovaries (women), but also in the adipose tissue, adrenal glands, brain, skin, and bone [4]. For example, adipose tissue becomes an important source of estrogens in postmenopausal women and obese men [4]. Higher body mass index (BMI) and lower physical activity levels have been positively associated with higher levels of circulating estrogens in postmenopausal women and men [40, 41]. Sex hormones are

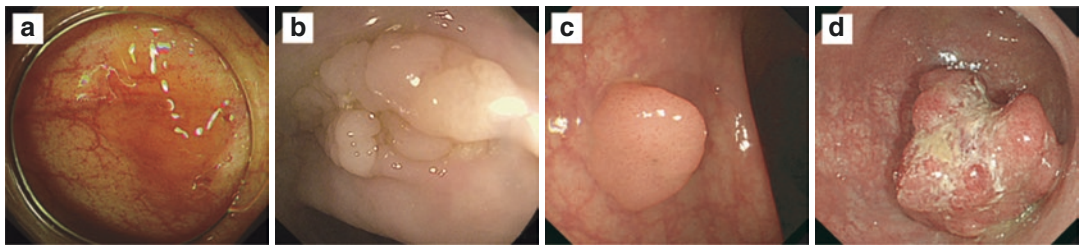

Fig. 20.7 Right-sided tumors (**a** and **b**) are more difficult to diagnose by colonoscopy because of their flat shape neoplasia compared to the polyp type neoplasia from left-sided tumors (**c** and **d**).

mainly bound to albumin in the plasma and to sex hormone binding globulin (SHBG). Only 1–3% of circulating sex hormones are unbound, and this fraction is considered to be most biologically active. Both sexes produce the same sex hormones with differential effects depending on circulating concentration, receptor expression, and hormone-specific interactions with target organs [4]. Progesterone has also been considered as a potential contributor to CRC protection. In general, normal serum progesterone levels are lower in males than females; however, males have similar progesterone levels (~1 ng/ml) as postmenopausal women, and as women at the beginning of their menstrual cycle [4]. Progesterone levels increase in women in the middle of the menstrual cycle from 5 to 20 ng/ml, and in pregnancy from 11 to 90 ng/ml [42]. Recent evidence implicated that progesterone reduced CRC but this seems to be additive to estrogen signaling via the estrogen receptor ERβ [43], and a protective role for progesterone looks like to be specific to postmenopausal incidence of CRC [44]. It looks like that the effect of progesterone on the CRC is rather minor so far. Among these sex hormones, the mechanisms of estrogen with its receptors and testosterone on the development of CRC are being actively discovered.

20.3.1.1 Estrogen

Estrogen acts through estrogen receptors (ERs, ERα and ERβ) that have genomic and non-genomic effects [45]. Genomic effects appear through estrogen-responsive elements located at the promotor of target genes. In addition, it affects transcription factors such as activating protein-1 (AP-1) and stimulating protein-1 (Sp-1) [45]. Furthermore, non-genomic effects are medicated through protein-kinase cascades. Many steroid hormones including estrogen produce both rapid and latent biological actions, which can be divided into membrane-initiated non-genomic effects (seconds – minutes) and nuclear genomic responses (hours-days) [46]. Genomic responses mainly involve estrogen binding to the major wild-type estrogen isoforms ERα (encoded by ESR1) and ERβ (encoded by ESR2) in the cytosol (with release from heat shock proteins) or directly in the nucleus to produce receptor dimerization and interact with cofactors to induce gene transcription and protein synthesis [4]. Non-genomic rapid responses to steroid hormones (RRSH) on the other hand involve estrogen binding to a membrane-associated estrogen receptor followed usually by transactivation of other membrane receptors (G-proteins or EGFR) to induce rapid protein kinase signaling, which modulate cellular processes such as calcium signaling, pH, ion channel activity, and metabolic pathways [47].

20.3.1.1.1 17β-Estradiol Reduces Inflammation and Modulates Antioxidant Enzymes in Colonic Epithelial Cells (CCD841CoN)

Inflammation is a very important mechanism to provide the tumor microenvironment and to provoke the cancer in the presence of other precancerous conditions. As estrogen prevents the development of CRC; thus, we investigated whether estradiol treatment reduces inflammation in CCD841CoN, a female human colonic epithelial cell line, and uncovered underlying mechanisms of estradiol effects on this inflammation [48]. For this 17β-estradiol (E2), effect was measured by Western blot after inducing inflammation of CCD841CoN by tumor necrosis factor alpha (TNF-α) [48]. We found that ERα expression has no significant change after E2 treatment (Fig. 20.8a) but E2 treatment consistently increased ERβ expression from 1 nM concentration of E2 (Fig. 20.8b, $p < 0.05$). In addition, E2 treatment for 48 h significantly elevated the expression of anti-oxidant enzymes, heme oxygenase-1 (HO-1) ($p < 0.05$) (Fig. 20.8c), and NAD(P)H-quinone oxidoreductase-1 (NQO1) ($p < 0.05$) [48] (Fig. 20.8d). TNF-α treatment significantly increased the level of activated nuclear factor-κB (NF-κB) ($p < 0.05$), and this increase was significantly suppressed by the treatment of 10 nM of E2 ($p < 0.05$) (Fig. 20.8e). Furthermore, E2 treatment ameliorated TNF-α-induced cyclooxygenase-2 (COX-2) expression ($p < 0.05$) (Fig. 20.8f). However, 4-(2-phenyl-5,7-bis(trifluoromethyl)pyrazolo(1,5-a) pyrimidin-3-yl)phenol (PHTPP), antagonist of ERβ, removed the inhibitory effect of E2 in the TNF-α-induced COX-2 expression ($p = 0.05$). In the next, we evaluated the Kelch-like ECH-associated protein-1 (Keap1)/nuclear factor ery-

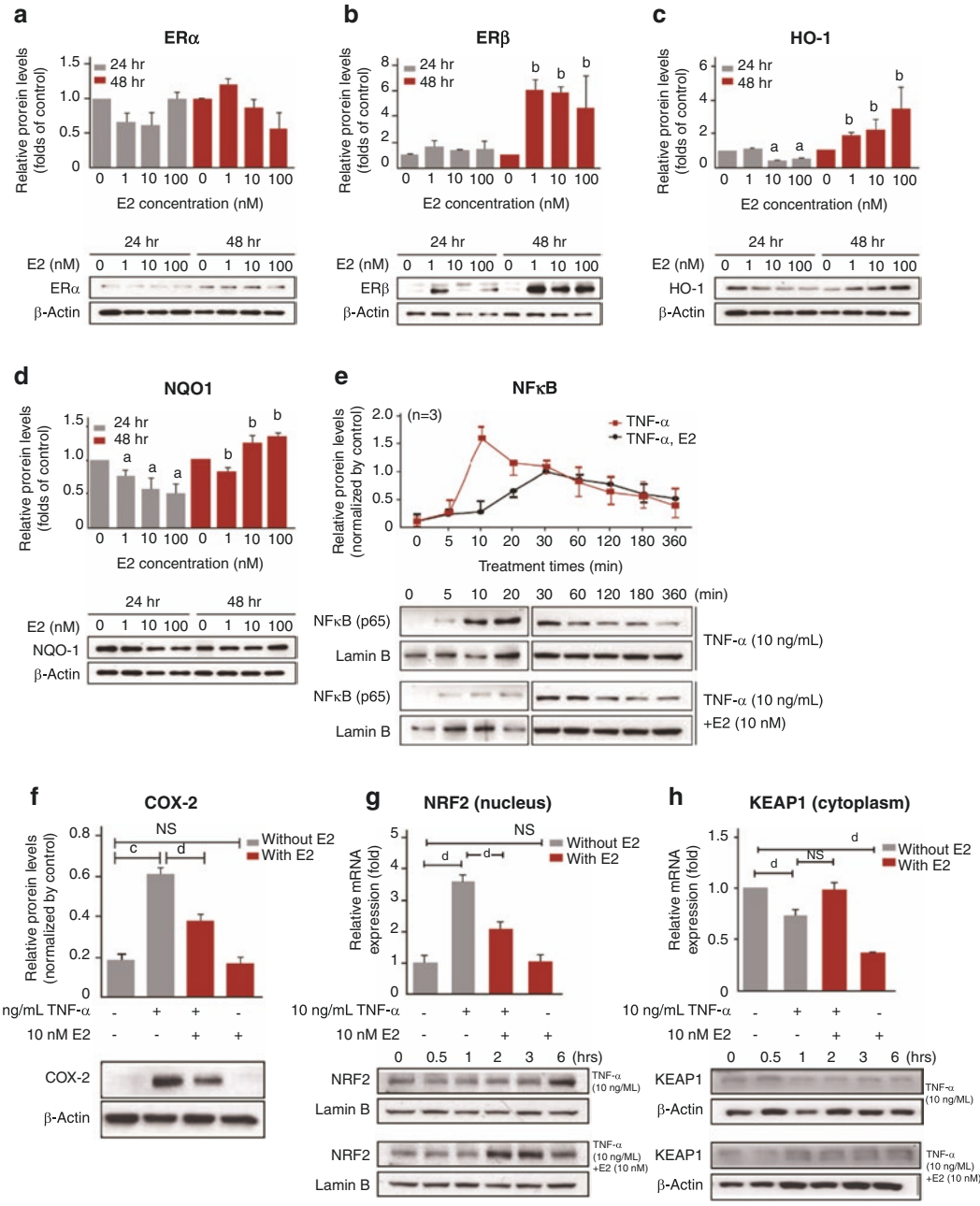

Fig. 20.8 17β-estradiol (E2) reduces inflammation and modulates antioxidant enzymes following tumor necrosis factor alpha (TNF-α)-induced inflammation in colonic epithelial cells (CCD841CoN). (**a**) ERα expression has no significant change after E2 treatment. (**b**) E2 treatment consistently increased ERβ expression from 1 nM concentration of E2 ($p < 0.05$). (**c**) E2 treatment for 48 h significantly elevated the expression of heme oxygenase-1 (HO-1) ($p < 0.05$). (**d**) E2 treatment for 48 h also significantly elevated the expression of NAD(P)H-quinone oxidoreductase-1 (NQO1) ($p < 0.05$). (**e**) TNF-α treatment significantly increased the level of activated nuclear factor-κB (NF-κB) ($p < 0.05$), and this increase was significantly suppressed by the treatment of 10 nM of E2 ($p < 0.05$). (**f**) E2 treatment ameliorated TNF-α-induced cyclooxygenase-2 (COX-2) expression ($p < 0.05$). (**g**) The protein expression level of nuclear factor erythroid 2-related factor 2 (NRF2), a transcriptional factor-related pathways, increased in the presence of 10 ng/mL TNF-α/E2 for 2–3 h and then NRF2 expression was inhibited at 6 h. (**h**) The protein expression level of Kelch-like ECH-associated protein-1 (KEAP1) showed no significant difference according to the treatment of TNF-α and E2. *NS* is not significant, $^{a}p < 0.05$ compared with the control (0, white bar) of target gene expression, $^{b}p < 0.05$ compared with the control (0, black bar) of target gene expression, $^{c}p < 0.001$ (adapted from Son et al. [48])

throid 2-related factor 2 (Nrf2) signaling pathway because they regulate anti-inflammatory gene expression to suppress the progression of inflammation [49]. The protein expression level of NRF2, a transcriptional factor, increased in the presence of 10 ng/mL TNF-α/E2 for 2–3 h and then this effect disappeared 6 h (Fig. 20.8g). In contrast, the protein expression level of KEAP1 showed no significant difference according to the treatment of TNF-α and E2 (Fig. 20.8h). This upregulation of NRF2 by E2 during 2–3 h after treatment is consistent with a previous study that reported the stimulation of Nrf2-Keap1 antioxidant defense in human neuroblast cell line [50]. The persistent expression of KEAP1 with little variation during TNF-α/E2 treatment was in accordance with previous results [51]. These results suggested that estrogen inhibits inflammation through downregulation of NF-κB and COX-2 expression and induction of anti-oxidant enzymes such as HO-1 and NQO1 which is downstream of Nrf2 in female human colonic epithelial cell lines [48].

20.3.1.1.2 Preventive Mechanism of Estradiol in an AOM/DSS-treated Mouse Model of Colorectal Cancer and Dual Role of Nrf2

Our team showed the protective roles of estradiol in colorectal tumorigenesis by showing more tumor multiplicities in AOM/DSS-treated male mice compared to AOM/DSS-treated female mice [15, 52]. Estradiol increased Nrf2 activity in breast cancer cell line [53] and in colonic epithelial cells (CCD841CoN) [48]. Yet in CRC vivo model, there was no comprehensive knowledge about estradiol as an upstream regulator of Nrf2. Protein kinase C delta (PKCδ), an important mediator in the $G\alpha_{13}$ signaling pathway, promotes Nrf2 activity [54]. In addition, PKC has been closely related to the protective effect of estradiol on vascular reactivity after shock in female rats [55]. Furthermore, estradiol-induced protein synthesis in mouse uterine epithelial cells was also mediated through the PKC signaling pathway [56]. Estradiol increased the mRNA level of PKCδ in the colonic epithelium of rats [57]. Thus, the $G\alpha_{13}$-PKCδ signaling pathway could be an upstream regulator of Nrf2 in CRC, and estradiol might play a role in this cascade. There are several suggested mechanisms of the Nrf2-mediated prevention of inflammation and tumorigenesis [15]. First, the activation of Nrf2 and cross-talk between Nrf2 and nuclear factor-kappa B (NF-κB) downregulate pro-inflammatory signaling by suppressing NF-κB directly [58]. Second, Nrf2 is one of the most essential transcription factors that regulate the expression of anti-oxidant enzymes [59]. Lastly, the close relationship of Nrf2 with the activating mechanism of the NLRP3 inflammasome was recently reported [60]. Considering the importance of Nrf2 in NLRP3 inflammasome activation [60], Nrf2 activation might lead to immune modulation through caspase-1-related activities, such as pyroptosis [61].

Inflammation is an important factor in the pathophysiology of colitis-associated and sporadic CRC. For example, Salerio et al. demonstrated the higher levels of inflammatory cytokines and polyp development at weeks 9 and 16 in AOM/DSS-treated estrogen receptor β (ERβ) knockout mice, compared to wild-type mice [62]. However, almost no studies have thoroughly evaluated the early inflammation stage of tumorigenesis, since in most of the studies, the animals were sacrificed after adenoma formation. From this background, we hypothesized that the observed sex difference in CRC incidence may be due to estradiol-mediated downregulation of inflammation, which might somehow affect the CRC cascade [15]. To explore this hypothesis, we assessed the temporal role of Nrf2 in modulating inflammation and carcinogenesis through the regulation of the NF-κB-mediated pro-inflammatory pathway, anti-oxidant enzymes, and the Nod-like receptor protein 3 (NLRP3) inflammasome [15]. This Nrf2/NLRP3 inflammasome/IL-1β-mediated pyroptosis might trigger the elimination of precancerous cells during inflammation and play a key role in preventing carcinogenesis in the presence of estradiol. AOM/DSS-treated male and female mice were sacrificed at weeks 2, 10, and 16, to assess estrogen effects on colitis and carcinogenesis [15] (Fig. 20.9). Compared with AOM/DSS-treated

male mice (M-AOM/DSS group), AOM/DSS-treated male mice with estradiol administration (M-AOM/DSS + estr group) displayed at week 2 significantly decreased severity of colitis. At weeks 10 and 16, AOM/DSS-treated female mice (F-AOM/DSS group) and the M-AOM/DSS + estr group showed significantly lower tumor multiplicity compared with the M-AOM/DSS group. At week 2, F-AOM/DSS group had a lower level of NF-κB expression and a higher level of Nrf2 expression, compared to the M-AOM/DSS group [15]. After confirming the sex difference in CRC development by showing that the F-AOM/DSS group has significantly

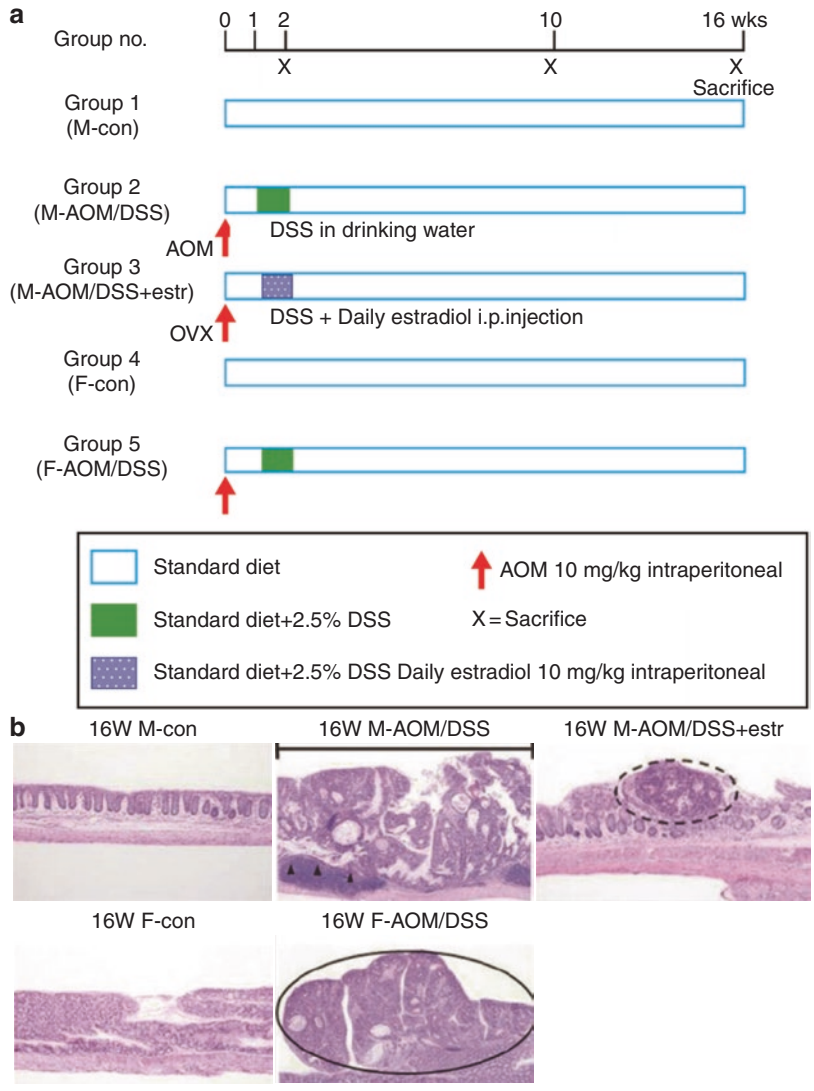

Fig. 20.9 Estradiol prevents wasting disease progression in AOM/DSS-induced colitis. (**a**) Scheme for the experimental course of AOM/DSS promoted colitis-associated tumorigenesis. The mice were injected AOM on day 0. DSS in drinking water (2.5%) and estradiol supply was provided from day 7 to 13. Mice were sacrificed at week 2, 10, and 16. (**b**) Histopathologic findings of the colonic mucosa (H&E, ×200) at week 16. (**c**) Tumor incidence is presented in each group. $^{*}p < 0.05$ compared to control, $^{\dagger}p < 0.05$ compared to AOM/DSS group, $^{\ddagger}p < 0.05$ between estradiol-treated group and female AOM/DSS group. *M* male, *F* female, *AOM* azoxymethane, *DSS* dextran sulfate sodium, *estr* estradiol (adapted from Son et al. [15])

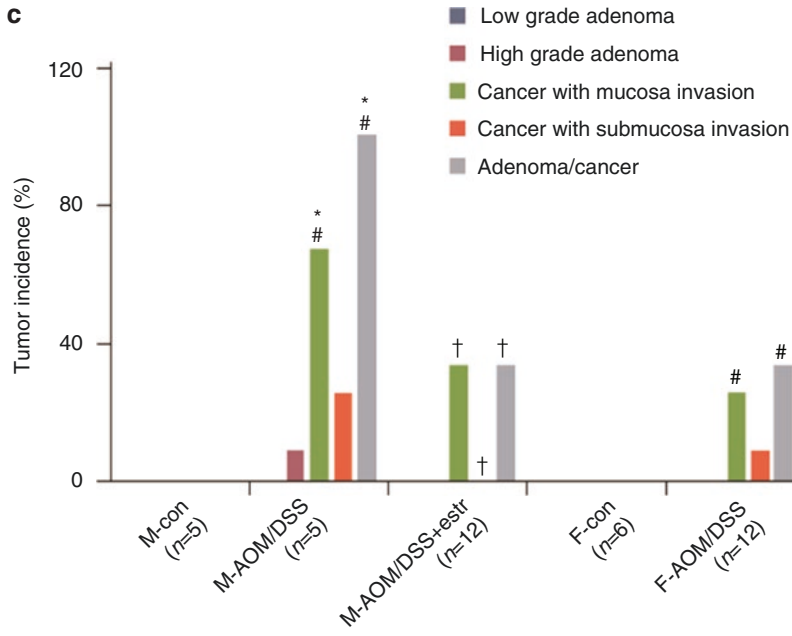

Fig. 20.9 (continued)

lower tumor multiplicity and incidence compared with the M-AOM/DSS group, we further investigated the underlying anti-cancer mechanism of estradiol. At week 2, expression levels of NF-κB and its related mediators decreased in the M-AOM/DSS + estr group, while levels of Nrf2 and Nrf2-related anti-oxidant enzymes increased. In addition, estradiol significantly increased NLRP3 inflammasome expressions in AOM/DSS-treated male mice. In contrast, at weeks 10 and 16, Nrf2 and its-related anti-oxidant enzymes and NLRP3 inflammasome were highly expressed in M-AOM/DSS group and in F-AOM/DSS group, who developed cancer. Our data suggest that estradiol inhibits the initiation of CRC by regulating Nrf2-related pathways and demonstrated a dual role of Nrf2 in modulating inflammation and carcinogenesis through the regulation of the NF-κB-mediated pro-inflammatory pathway, anti-oxidant enzymes, and NLRP3 inflammasome. In this research, we focused on week 2, which is the active DSS-induced inflammation stage [63], just after the completion of estradiol administration, and several weeks before the AOM/DSS-induced tumorigenesis. The severity of inflammation at week 2 was associated with tumor formation at weeks 10 and 16. Our study clearly demonstrates the importance of early inflammatory control by the administration of estradiol to AOM/DSS-treated male mice, to confirm the role of estradiol for CRC prevention. In addition, the M-AOM/DSS + estr group was compared with the F-AOM/DSS group to check any differences between exogenous and endogenous estradiol. This approach strongly supports the inhibitory effect of estradiol on inflammation and inflammation-induced tumorigenesis, and also notably uncovers its underlying mechanism of estradiol in three aspects: (1) NF-κB-related pro-inflammatory mediators, (2) Nrf2-related anti-oxidant enzymes, and (3) NLRP3 inflammasome [15]. The NF-κB signaling pathway is highly involved in inflammation and cancer development, especially in colitis-associated CRC [64]. In our study, estradiol inhibited the NF-κB signaling pathway involving iNOS, COX-2, IL-6, and TNF-α during the DSS-induced inflammation stage of AOM/DSS-induced colon tumorigenesis [15]. Furthermore, the concomitant increased expression of $G\alpha_{13}$, PKCδ, and

Nrf2 by estradiol administration in AOM/DSS-treated male mice during the DSS-induced inflammation stage supports the correlation between the suppression of NF-κB signaling and the estradiol-induced activation of $G\alpha_{13}$/PKCδ/Nrf2 pathway [15]. ERs inhibit the NF-κB pathway by the modulation of upstream signaling or the transcriptional activation of NF-κB in various cell lines [65]. Nrf2 inhibition of NF-κB activity is well known. $G\alpha_{13}$ strengthens ERα activity [66], and estradiol regulates the activity of PKCδ [57] and Nrf2 [53].

Nrf2 signaling was significantly upregulated after tumors developed (weeks 10 and 16), in the M-AOM/DSS group, and this suggest that Nrf2 and anti-oxidant enzymes might play a role in promoting tumor progression [15]. Several studies reported the possibility of the dual role of Nrf2 in tumor prevention and progression [67]. Satoh et al. showed that Nrf2 activation in cancer cells enhances tumor malignancy, while Keap1-knockdown mice having high expression of Nrf2 are more resistant to urethane-induced carcinogenesis [67]. Similar to Nrf2, we found two facets of NLRP3 inflammasome. Although NLRP3 inflammasome is a well-established target of NF-κB, its expression is inversely related to NF-κB expression at week 2. This indicates that it might have different roles from NF-κB, such as inducing pyroptosis in the DSS-induced inflammation stage. In contrast, it has been reported that once tumor formation is initiated, NLRP3 inflammasome-induced IL-1β and IL-18 modulate immunity in the tumor microenvironment and promote cancer progression [68]. A significant increment of NLRP3 and caspase-1 expression in the F-AOM/DSS cancer group compared to the F-AOM/DSS non-cancer group in our study also supports tumor promotion by the NLRP3 inflammasome [15].

The collective present and prior [54, 61, 66] data support the proposal that the regulatory mechanism of estradiol in colitis-associated CRC depends on sex, and the timing of DSS-induced inflammation and carcinogenesis [15] (Fig. 20.10). At the peak of inflammation at week 2, estradiol appears to induce inflammasome activation through $G\alpha_{13}$ protein subunits. $G\alpha_{12}$ and $G\alpha_{13}$ have potentiated estradiol-bound ERα activity [66]. However, despite the functional overlap between $G\alpha_{12}$ and $G\alpha_{13}$, only $G\alpha_{13}$ regulates NRF2 via PKCδ [54]. NRF2 mediates inflammasome activation through the transcription of as-yet unknown genes. NLRP3 inflammasome activation induces pyroptosis to eliminate precancerous cells [61]. NRF2 inhibits NF-κB, which is activated by inflammatory activators through toll-like receptor (TLR) signaling and reactive oxygen species. Ultimately, estradiol prevents carcinogenesis, whereas in the absence of estradiol, a cancer-inducing microenvironment is created through NF-κB activation. When precancerous cells are not completely eliminated, cancer progresses through both the $G\alpha_{12}$ and $G\alpha_{13}$ protein subunits. $G\alpha_{12}$ regulates the NF-κB-mediated signaling pathway [54, 69]. $G\alpha_{13}$ regulates NRF2 via PKCδ [54]. NRF2 promotes tumor progression by the activation of anti-oxidant enzymes and NLRP3 inflammasome [60]. Ultimately, NF-κB and NRF2 signaling pathways accelerate colonic carcinogenesis (Fig. 20.10).

20.3.1.1.3 Effects of 17β-Estradiol on Colorectal Cancer Development in the AOM/DSS-treated Mouse Model After Ovariectomy

In the next, we investigated whether ovariectomy in a female AOM/DSS mouse model increases colorectal tumorigenesis and whether tumorigenesis is reduced by estrogen supplementation after ovariectomy [70]. Experimental protocol for evaluating the effects of E2 on AOM/DSS-induced colitis and associated tumorigenesis is presented in Fig. 20.11a [70]. Initially, we expected AOM/DSS-induced inflammation at week 2 and carcinogenesis at weeks 10 and 16 to be more severe in ovariectomy (OVX) mice than in control mice. However, ovariectomy did not aggravate colitis-associated symptoms, including DAI score, colon shortening, and colitis severity, but rather decreased the levels of the inflammatory mediator MPO. A previous report showed that the serum level of testosterone (T), a major male sex hormone, was decreased alongside serum E2 levels in OVX mice compared to control mice [71]. We do not know the precise reason but OVX did not aggravate AOM/DSS-induced colitis at 2 weeks.

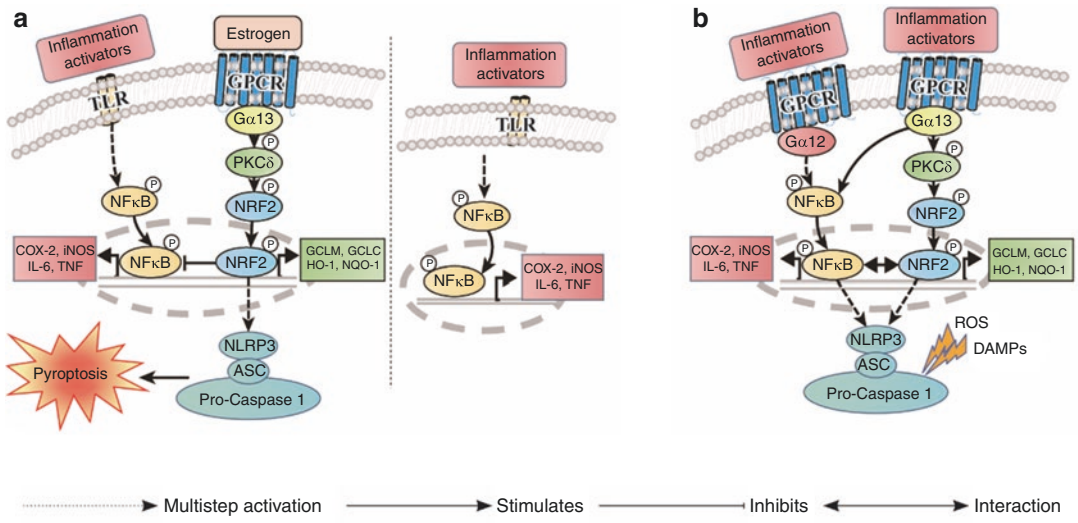

Fig. 20.10 Proposed regulatory mechanism of estrogen in colitis-associated CRC at week 2 (**a**) and at weeks 10 and 16 (**b**). (**a**) Estrogen induces inflammasome activation through $G\alpha_{13}$ protein subunits. $G\alpha_{12}$ and $G\alpha_{13}$ have potentiated estrogen-bound ERα activity. However, despite the functional overlap between $G\alpha_{12}$ and $G\alpha_{13}$, only $G\alpha_{13}$ regulates Nrf2 via PKCδ. Nrf2 mediates inflammasome activation through the transcription of as-yet unknown genes. NLRP3 inflammasome activation induces pyroptosis to eliminate precancerous cells. After eliminating precancerous cells, Nrf2 inhibits NF-κB and reactive oxygen species through the anti-oxidant enzymes. Ultimately, estrogen prevents carcinogenesis (Left Panel). In contrast, in the absence of estrogen, inflammation provides a cancer microenvironment through activation of the NF-κB pathway (Right Panel). (**b**) After unsuccessful elimination of precancerous cells, inflammation progresses to cancer at weeks 10 and 16. $G\alpha_{12}$ and $G\alpha_{13}$ regulate NF-κB and Nrf2 via PKCδ-mediated signaling pathway, respectively. Nrf2 promotes tumor progression by activation of anti-oxidant enzymes and NLRP3 inflammasome. Ultimately, NF-κB and Nrf2 signaling pathways accelerate carcinogenesis (adapted from Son et al. [15])

Interestingly at weeks 10 and 16, ovariectomy significantly increased tumor number and incidence rate in only the proximal colon after AOM/DSS treatment (F_AOM/DSS vs OVX_AOM/DSS), and these increases were significantly reduced by E2 supplementation (OVX_AOM/DSS vs OVX_AOM/DSS/E2) [70] (Fig. 20.11b, c). However, ovariectomy did not affect CRC development in the distal colon (F_AOM/DSS vs OVX_AOM/DSS) [70] (Fig. 20.11b, c). Tumor development within the proximal colon is closely associated with female sex, age older than 68 years, hypermethylation, and MSI-high status [8]. Therefore, it is expected that females have a higher risk of developing proximal (right-sided) colon cancer than do males, and this type of colon cancer is more aggressive than distal (left-sided) colon cancer [8]. Furthermore, Missiaglia et al. and Wang et al. recently reported that proximal and distal colon cancers differ in terms of molecular, pathological, and clinical features and cancer-specific survival rates. According to previous reports, proximal cancer is more often mucinous and MSI-high, and key tumorigenic pathways are more often mutated, such as mutated $BRAF^{V600E}$, regardless of histological type [34]. Additionally, stage II proximal cancers showed a lower cancer-specific mortality than distal cancers at the same stage [72]. In contrast to proximal cancers, distal cancers more often harbor chromosome instability and EGFR or human epidermal growth factor receptor 2 (HER2) amplifications and more frequently overexpress epiregulin [34]. These data strongly support the pivotal role of estrogen in inflammation and inflammation-mediated carcinogenesis, especially tumor development in the proximal colon, as shown in OVX mice.

For the evaluation for the underlying mechanism, clinical symptoms and histological severity

of colitis and the levels of inflammatory mediators were evaluated in the colon of AOM/DSS-treated OVX mice. At week 2, E2 administration to AOM/DSS-treated OVX mice attenuated the histological severity of colitis by decreasing the protein and/or mRNA levels of ERα and NF-κB-related mediators (i.e., COX-2, TNF-α, and IL-6) and by enhancing estrogen receptor beta (ERβ) and nuclear Nrf2 protein expression and the mRNA expression of related antioxidant enzyme genes (i.e., HO-1, GCLC, GCLM, and NQO1) [70]. NF-κB, a well-known mediator of inflammatory responses, plays a pivotal role in carcinogenesis and is emerging as a link between

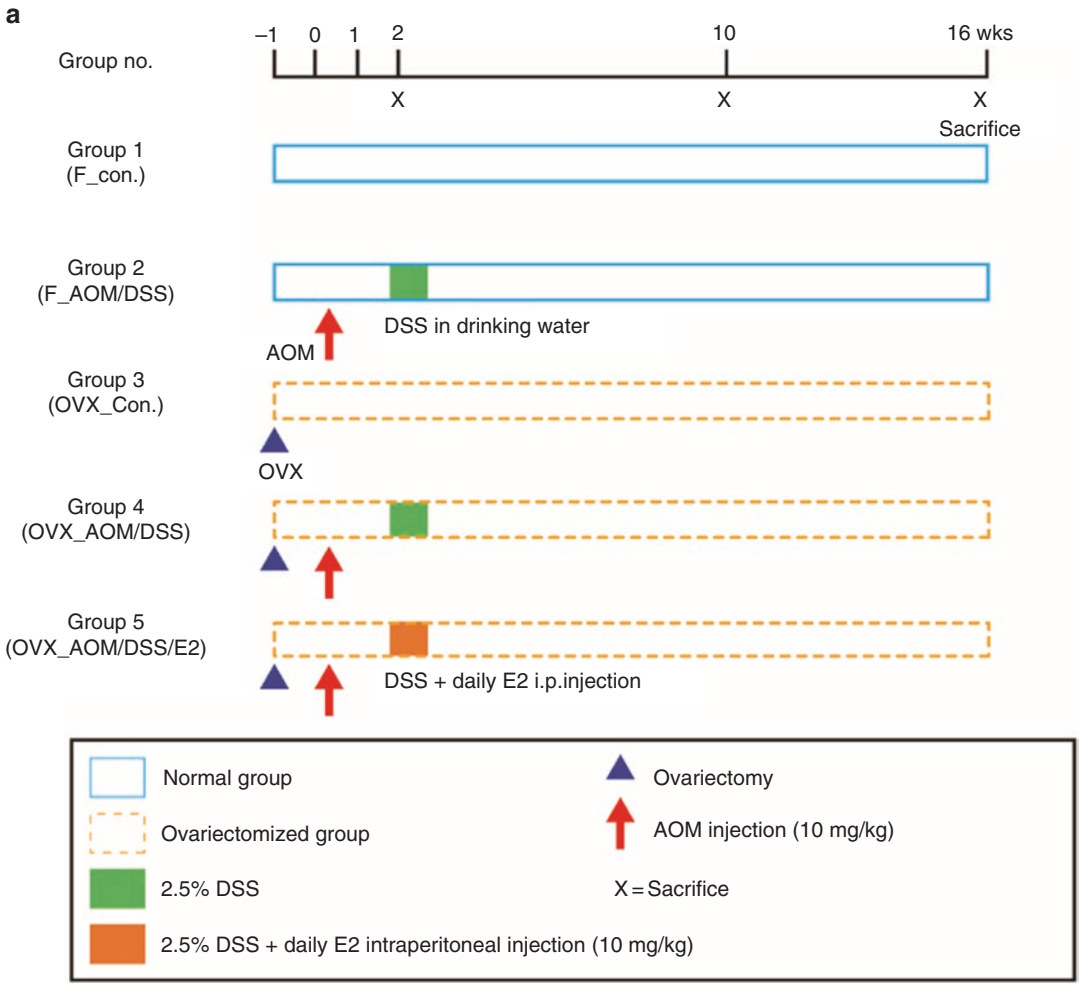

Fig. 20.11 Ovariectomy and 17β-estradiol administration with AOM/DSS treatment in female ICR mice. (**a**) Experimental protocol for evaluating the effects of E2 on AOM/DSS-induced colitis after ovariectomy. One week after ovariectomy, animals were enrolled in the AOM/DSS protocol. The mice were injected with AOM on day 0 and were provided DSS in drinking water (2.5%) and E2 supplementation from day 8 to 14. Mice were sacrificed at weeks 2, 10, and 16. (**b**) Tumor incidence at weeks 10 and 16. (**c**) Representative histological images after H&E staining at weeks 10 (upper panel) and 16 (lower panel). Adenoma is indicated by a dashed-line circle, and adenocarcinoma is indicated by a solid-line circle and a bar (H&E, ×200). *F* female, *OVX* ovariectomized, *E2* 17β-estradiol, *AOM* azoxymethane, *DSS* dextran sulfate sodium, *F_Con* female control mice, *F_AOM/DSS* female mice treated with AOM/DSS, *OVX_Con* ovariectomized female control mice, *OVX_AOM/DSS* ovariectomized female mice treated with AOM/DSS, *OVX_AOM/DSS/E2* AOM/DSS-treated ovariectomized female mice administered E2. *$p < 0.05$ for comparison between two groups (adapted from Song et al. [70])

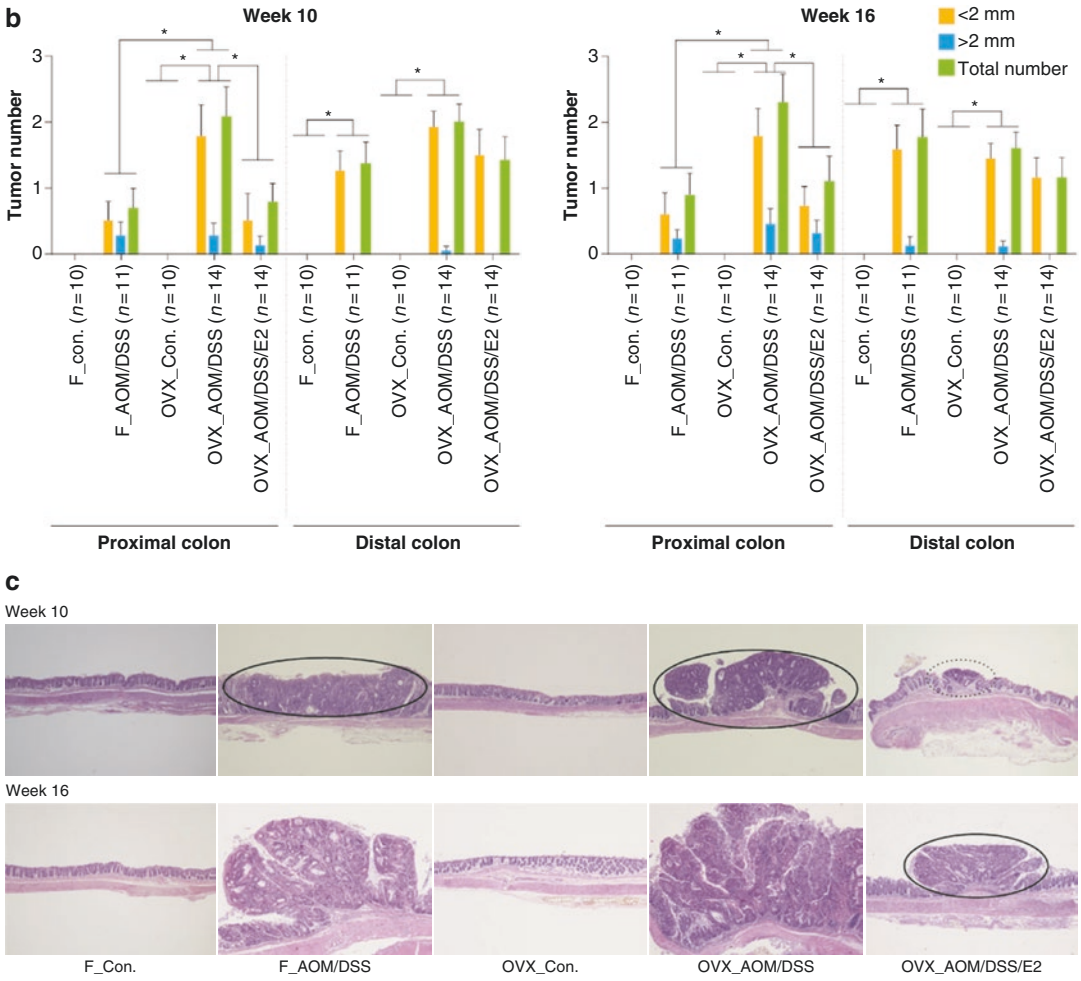

Fig. 20.11 (continued)

inflammation and cancer [64]. It is highly activated at inflammatory sites in diverse diseases, including inflammatory bowel disease [73], and can induce the transcription of proinflammatory cytokines, growth factors, chemokines, and anti-apoptotic genes [74]. In addition, NF-κB is well known to induce the expression of COX-2, a key mediator of the inflammatory process [75]. In this OVX study, E2 treatment decreased the levels of NF-κB-regulated proinflammatory cytokines (i.e., TNF-α and IL-6) and COX-2 gene expression compared to the corresponding control during the inflammation (week 2) and tumorigenesis (weeks 10 and 16) stages [70]. Furthermore, nuclear Nrf2 protein levels and the mRNA expression of Nrf2 and antioxidant enzyme genes (i.e., HO-1, GCLC, GCLM, and NQO1) were significantly increased by E2 treatment compared to the corresponding control at week 2 [70]. These data suggest that the increase in Nrf2 and antioxidant enzyme gene expression by E2 supplementation in the OVX_AOM/DSS group blocked the expression of NF-κB-regulated proinflammatory cytokines (i.e., TNF-α and IL-6) and COX-2. Taken together, endogenous estrogen in females protects against the development of proximal colon cancer, and exogenous E2 replacement in OVX female mice showed protective effects against AOM/DSS-induced colitis and carcinogenesis.

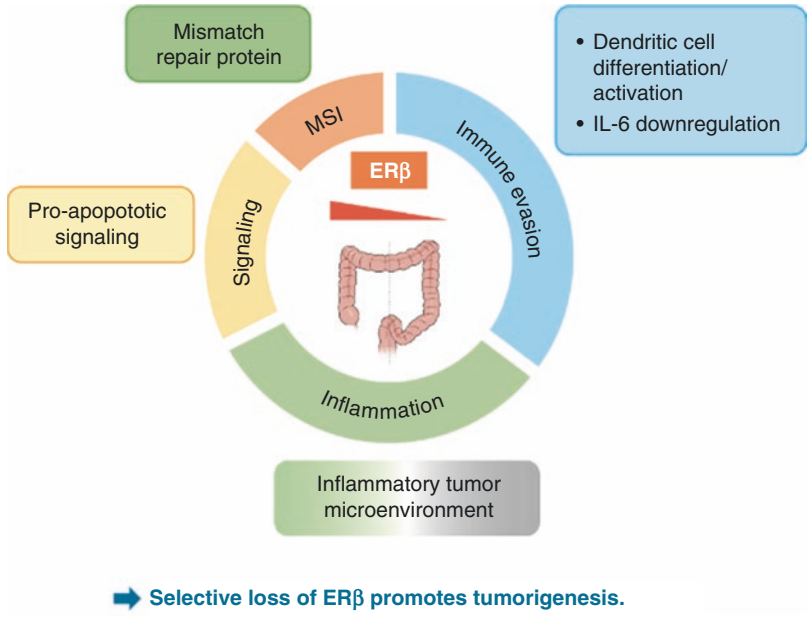

Fig. 20.12 Estrogens regulate the cellular effects through their intracellular receptors, estrogen receptors (ER)α and ERβ. ERβ showed tumor-suppressive function in CRC through activation of pro-apoptotic signaling, regulation of mismatch repair proteins, and modulation of the inflammatory tumor microenvironment (adapted from Caiazza et al. [79])

20.3.1.2 Estrogen Receptors (Membrane Estrogen Receptor and G Protein-Coupled Estrogen Receptor)

The receptors involved in transducing rapid non-genomic responses to estrogen are the membrane estrogen receptor (mER, ERα and ERβ) and the G protein-coupled estrogen receptor (GPER, encoded by the *GPER1* gene) [4]. Most of the rapid actions of estrogen have been shown to be transduced by mER [76], whereas GPER appears to become biologically important as an estrogen receptor in tissues where the expression of ER isoforms is low or undetectable [77]. Significant biologically relevant cross-talk has been demonstrated between genomic and non-genomic signaling pathways [78]. Membrane-initiated rapid responses to estrogen have been shown to influence the latent genomic responses (for example by MAPK phosphorylation of the ligand-receptor complex to facilitate nuclear translocation and phosphorylation of transcription factor signaling such as PKA-CREB) and vice versa genomic effects can regulate rapid responses through the synthesis of protein kinases essential for rapid actions in the cytosol [4].

20.3.1.2.1 Membrane Estrogen Receptors

The protective role of estrogen in the female against CRC has been mainly associated with expression levels of the ERβ in intestinal epithelial cells [79, 80]. That is, ERβ is the prevalent estrogen receptor in normal colon mucosa and shows a significantly reduced expression in CRC [81]. ERβ showed tumor-suppressive function in CRC through activation of pro-apoptotic signaling, regulation of mismatch repair proteins, and modulation of the inflammatory tumor microenvironment [79] (Fig. 20.12). Thus, selective loss of ERβ within the large intestine promotes tumorigenesis [79, 81] (Fig. 20.12). That is, the ERβ1, ERβ2, and ERβ5 isoforms are expressed in the colon with variable levels along the crypt axis [82] and are reduced in tumor cells compared to normal colon [83, 84]. The experimental overexpression of ERβ in colon cancer cells showed that ERβ inhibits proliferation by blocking the cell cycle in the G1-S phase [85]

and stimulating apoptosis [86]. Moreover, ERβ induces anti-inflammatory signaling in CRC cells [87]. Other protective mechanisms attributed to ERβ in the colon include upregulation of tight junction proteins occludin (OCLN) and JAMA (F11R) to preserve homeostasis of paracellular permeability [88]. Our team also reported that the mRNA expressions of intestinal barrier-related molecules (Zonula occludens-1 [ZO-1], OCLN, and Claudin4 [CLDN4]) were decreased by AOM/DSS-treatment; and this inhibition was rescued by 17β-estradiol supplementation [89]. ERβ1 is the most highly expressed estrogen receptor in the healthy colonic epithelium, and the expression of ERβ1 is reduced in tumor cells compared to normal colon [90, 91]. Sustained ERβ1 expression in CRC correlates with better prognosis and patient survival, whereas loss of ERβ1 expression is correlated with worse prognosis [92]. Estrogen has been shown to increase ERβ levels, and this is a likely mechanism by which estrogen confers protection against CRC [93].

20.3.1.2.2 G Protein-Coupled Estrogen Receptor (GPER)

In addition, the protective estrogen activity in CRC in the absence of ER is explained by the role of membrane-bound GPER [94, 95]. Diverse functions of GPER in the colon include the regulation of visceral hypersensitivity and gut motility, immune responses in inflammatory bowel diseases (IBD) [96, 97], and the modulation of cell migration and proliferation in CRC cell lines [98]. GPER is known to stimulate gut motility; thus, it can prevent the possible effect of chronic constipation on CRC [99]. In addition, a sex-dependent regulation of GPER expression and signal transduction for mucosal inflammation has been proposed in IBD such as Crohn's disease and ulcerative colitis [100] which can provoke CRC, especially in male. Estrogen is known to produce a rapid non-genomic anti-secretory response in colon, which is both female sex-dependent but not observed in males [57, 101]. Thus estrogen and GPER modulate key physiological functions in the intestine [4]. Thus when they are dysregulated, CRC neoplasm can develop. Taken together estrogen effects in advanced CRC tumors may be transduced via GPER given the relative absence of expression of ERα or ERβ in CRC patients and cell lines studied [4]. Strangely GPER has been described as a tumor promoter in certain cancers such as breast cancer via activation of EGFR, STAT5, and MAPK/extracellular regulated kinase (ERK) pathways [102]. However, in CRC, the expression of GPER is reported to act variously as a tumor suppressor or promoter depending on the stage of the disease and expression levels of ER and GPER [103]. For instance, the expression of GPER was significantly decreased with increasing stage and lymph node metastasis of CRC patients [104]. That is, as colon cancer progresses to advanced stage disease, GPER expression was found to be greatly reduced in cancerous tissue compared to adjacent healthy colon and low GPER expression was associated with reduced survival [105]. Moreover, high GPER expression was associated with poor relapse-free survival in women with stage 3/4 but not in stage 1/2 CRC while there was no correlation of GPER expression in men with disease of any stage [18]. Taken together, the role of GPER in CRC looks like to be both sexually dimorphic and dependent on the stage of the disease [4]. Possible answers for these discrepancies might lie within the tumor microenvironment where metabolic signals may modulate the signaling pathways regulated by estrogen/GPER [4]. Sexual dimorphism in the biology of gene and protein expression, and in endocrine cellular signaling, underpins the sexual dichotomy in colon cancer summarized in Fig. 20.13 [4].

20.3.1.3 Testosterone and Orchiectomy-Associated Colorectal Cancer in the AOM/DSS-treated Mouse Model

Testosterone is the sex hormone in male. Here we evaluated the role of testosterone and androgen receptors and introduced our experiment regarding the effect of orchiectomy in the AOM/DSS-induced tumor numbers and incidence rates of CRC.

20.3.1.3.1 Testosterone and Androgen Receptors

Androgen receptors (ARs) have been reported to be expressed in CRC [106]. ARs are the binding

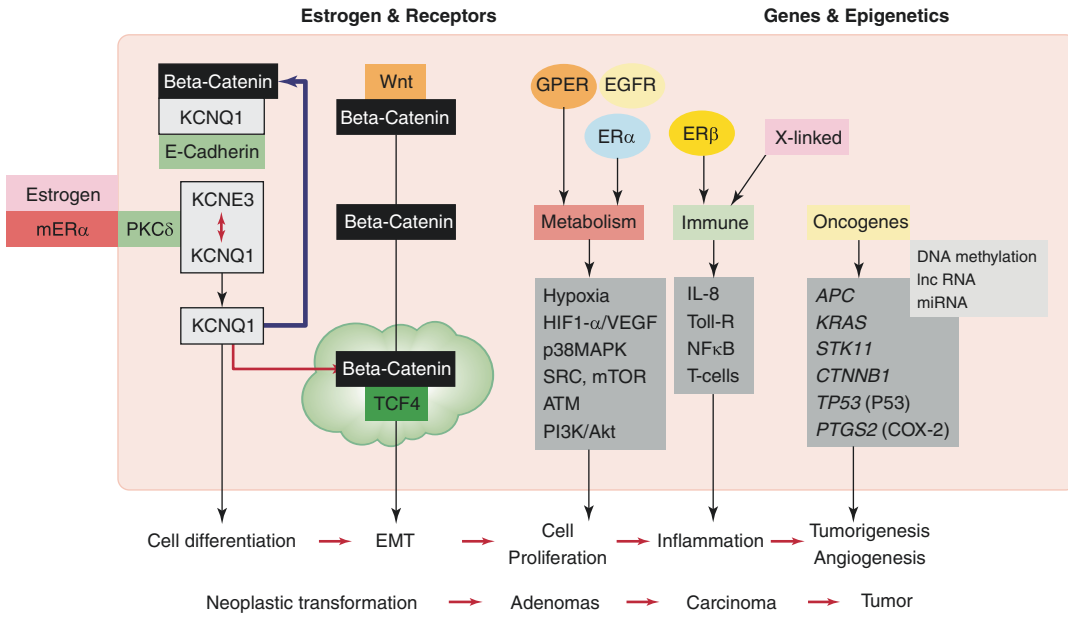

Fig. 20.13 Sexual dimorphism targets of estrogen signaling, receptors, and genes underpinning sex differences in the development of CRC. Estrogen, receptors, and genes modulate ion channels, metabolism, innate and adaptive immunity, and oncogene expression to activate non-genomic and genomic responses underpinning CRC development from neoplastic transformation, adenomas, and carcinoma to tumor (adapted from Abancens et al. [4])

site for dihydrotestosterone (DHT), and two isoforms of the AR, androgen receptor A (AR-A, 87-kDa) and androgen receptor B (AR-B, 110 kDa) [107]. Both of these were detected in healthy colonic mucosa whereas only AR-A was detected in neoplastic colonic mucosa [108]. It suggests that neoplastic colonic mucosa is characterized by loss of expression of the AR-B isoform, whereas AR-A expression is maintained [107]. As low levels of AR-A are normally detected in the fetal colon, the expression of AR-A in CRC may be indicative of loss of cell differentiation [107]. Membrane androgen receptors (mARs), cell-surface G-protein coupled receptors (GPCR) in colonic tumors signal via modulation of intracellular calcium or inositol 1,4-5-triphosphate second messenger pathways. Recently mARs have been reported to trigger apoptosis in neoplastic cells [108]. In addition, mARs were suggested to induce tumor regression, in the mice xenograft tumors and two colon cancer cell lines (Caco2 and HCT116 cells) [109]. Significant mAR expression was reported in xenograft tumor tissues and cell lines compared to healthy or nontransformed cells [109]. When fluorescence staining of Caco2 and HCT116 cells were treated with testosterone3-[O-carboxymethyl] oxime human serum albumin (testosterone-HSA) for 24 h apoptosis occurred via caspase-3 activation [109]. Taken together, mARs look like to play a role to regress the CRC contrary to our expectation. However, implantation of dihydrotestosterone in the APC PIR/+ rat and testosterone supplementation in the AOM mouse, along with castration, increased the number of adenomas [110]. Furthermore, a recent study in postmenopausal women in Japan [111] including 185 CRC patients and 361 controls showed that higher testosterone levels were significantly associated with CRC risk (odds ratio[OR] 2.1; 95% CI, 1.11–3.99). However, there are many contrary reports for the role of testosterone on the CRC in human studies. That is, there was no significant clinical correlation between testosterone concentrations and outcomes in CRC patients [112, 113]. For instance,

lower androgenicity in men, as a result of reduced androgen receptor activity by hypermethylation or lower circulating dehydroepiandrosterone sulfate, has been associated with increased CRC risk [114, 115]. A recent US study including 732 CRC patients and 1156 controls from 4 prospective cohorts reported that high testosterone levels in men were significantly associated with lower relative-risk for CRC (highest vs. lowest quartile 0.65) and showed no association in postmenopausal women [116]. Also, a prospective study evaluating 107,859 men diagnosed with prostate cancer from the American SEER-Medicare database has shown orchiectomy and long-term androgen-deprivation therapy (more than 25 months) were significantly associated with higher CRC risk (hazard ratio [HR] 1.37; 95% CI, 1.14–1.66, and HR 1.31; 95% CI, 1.12–1.53, respectively) [117]. As these are epidemiological observational studies, there may be many confounding factors leading to the different CRC risk associations in different populations [4]. Expression of the androgen receptor has also been explored for association with CRC risk. In a case-control study including 550 CRC patients and 540 controls, longer cytosine-adenine-guanine (CAG) repeats in the AR gene that reduce the transcription rates have been associated with higher CRC risk and lower 5-year median overall survival (HR 1.4; 95% CI, 1.04–1.79) in CRC patients [118]. In contrast, a German population–based study of 1798 CRC patients and 1810 controls reported no association between CAG repeats in AR and CRC prognosis [119]. Lastly, adding to this complexity, some smaller prospective population-based studies failed to detect any association of testosterone with CRC risk [113, 120]. In summary, the role of testosterone in CRC is not yet clear, but some of the compounding factors are age-dependent differential effects of the hormone, tumor stage, and tissue environment factors [4].

20.3.1.3.2 Orchiectomy Diminished the AOM/DSS-Induced Tumor Numbers and Incidence Rates in the Distal Colon

We investigated whether orchiectomy(ORX) in C57BL/6 male mice reduces colorectal tumorigenesis and whether testosterone administration increases tumorigenesis after orchiectomy in an AOM/DSS mouse model [17]. Experimental protocol for evaluating the effects of E2 on AOM/DSS-induced colitis (week 2) and associated tumorigenesis (week 13) is presented in Fig. 20.14a [17]. Orchiectomy significantly diminished the AOM/DSS-induced colitis indices, including disease activity index, colon shortening, and histological severity at week 2, and decreased tumor numbers, and incidence rates in the distal part of the colon increased following AOM/DSS administration at week 13; this reduction was reversed by testosterone supplementation (Fig. 20.14b, c). Most of colon tumors develop [63]. Similarly, AOM/DSS-treated male mice presented a higher tumor numbers than AOM/DSS-treated ORX males and females, especially tumors >2 mm in size in the distal colon [17]. Moreover, testosterone administration increased the tumor numbers compared to the AOM/DSS group. In addition, testosterone administration increased the development of submucosal invasive adenocarcinoma in males and females treated with AOM/DSS (Fig. 20.14b, c) [17]. Furthermore, endogenous and exogenous testosterone levels were identified as reasonable risk factors for developing distal colon submucosal invasive adenocarcinoma, based on multivariate and univariate logistic regression analyses [17]. According to a recent report, the molecular, pathological, and clinical characteristics of colon cancer and survival rates in CRC differ depending on the anatomical location [34]. Furthermore, there is a sex difference in the CRC location. That is, female CRC is more prevalent in the proximal colon, but in males, CRC is mainly located in the distal colon [70]. Furthermore, the depletion of endogenous estrogen by ovariectomy significantly increased tumor numbers and CRC incidence only in the proximal colon after AOM/DSS treatment compared to females treated with AOM/DSS, and these increments were strongly decreased following administration of exogenous E2 [70]. However, ovariectomy did not affect the occurrence of CRC in the distal colon [70]. These findings suggest a relationship between sex hormones and the anatomical location of CRC. The colon is anatomically divided into proximal (right

side) and distal (left side) part. Proximal colon cancer is frequently mucinous and has higher MSI, with major carcinogenic pathways such as mutant $BRAF^{V600E}$ mutated more often, regardless of the histological type [34]. In contrast, distal colon cancer is more frequently accompanied by chromosomal instability and epidermal growth factor receptor (EGFR) or human epidermal growth factor receptor 2 (HER2) amplification, often overexpressing epiregulin [34]. These present results strongly support the key role of testosterone in colitis and colon tumorigenesis, especially in the tumorigenesis of the distal part of the colon, as shown in ORX mice and female mice. Furthermore, it was confirmed that the ELISA level (MPO and IL-1β) and the mRNA expression of the inflammatory mediators (COX-2 and iNOS) were maintained at high levels in the tumors of the testosterone-treated group compared with AOM/DSS groups [70]. Taken together, endogenous and

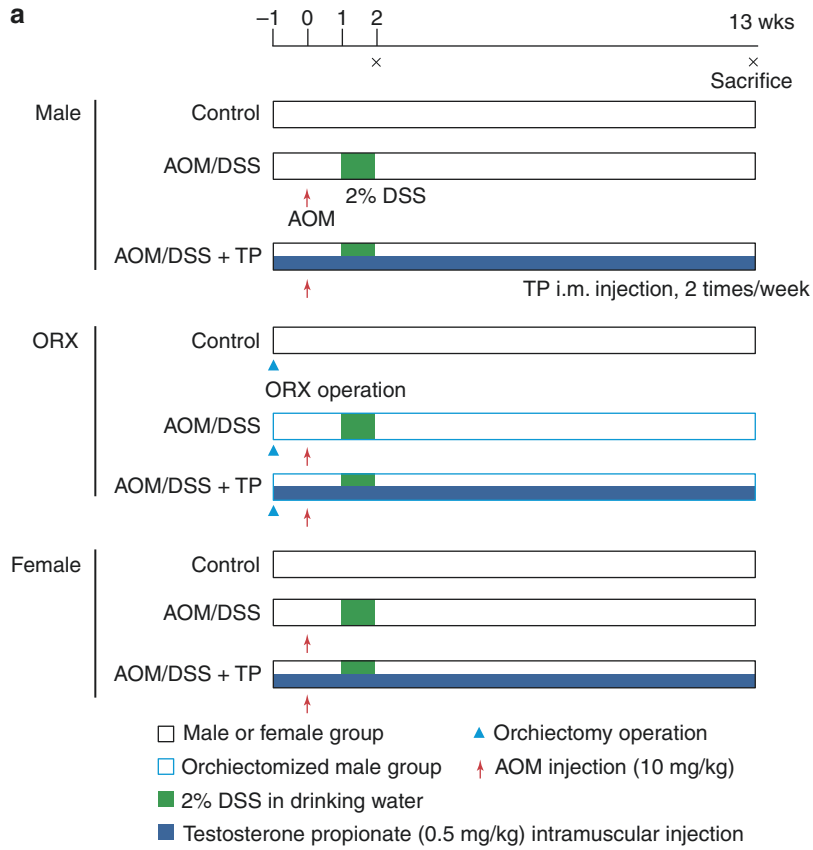

Fig. 20.14 Orchiectomy and testosterone administration in AOM/DSS-treated orchiectomy (ORX) and female C57BL/6 mice. (**a**) Scheme to evaluate the role of TP on AOM/DSS-induced colitis (week 2) and CRC (week 13). One week after orchiectomy, animals were enrolled in the AOM/DSS protocol. The mice were injected with AOM on day 0 and provided with DSS in drinking water (2%). TP administration was initiated on the day of surgery, administered twice a week by intramuscular (i.m.) injections. Mice were sacrificed at weeks 2 and 13. (**b**) Representative histological images after H&E staining at week 13. Adenocarcinoma is indicated by a circle and a bar. Submucosal invasion is indicated by a red arrow. Magnification, 40×. (**c**) Quantification of adenoma/adenocarcinoma incidence and invasion in each group by microscopic evaluation of colonic tissues at the carcinogenesis stage (at week 13). * $p < 0.05$ for Con *vs.* AOM/DSS, # $p < 0.05$ for AOM/DSS *vs.* AOM/DSS + TP, † $p < 0.05$ for male *vs.* ORX male, ‡ $p < 0.05$ for male *vs.* female; § $p < 0.05$ for ORX male *vs.* female. The statistical significance of the sum is shown at the top of the graph. *Con* control, *AOM* azoxymethane, *DSS* dextran sulfate sodium, *TP* testosterone propionate, *ORX* orchiectomized, *H&E* hematoxylin-eosin (adapted from Song et al. [17])

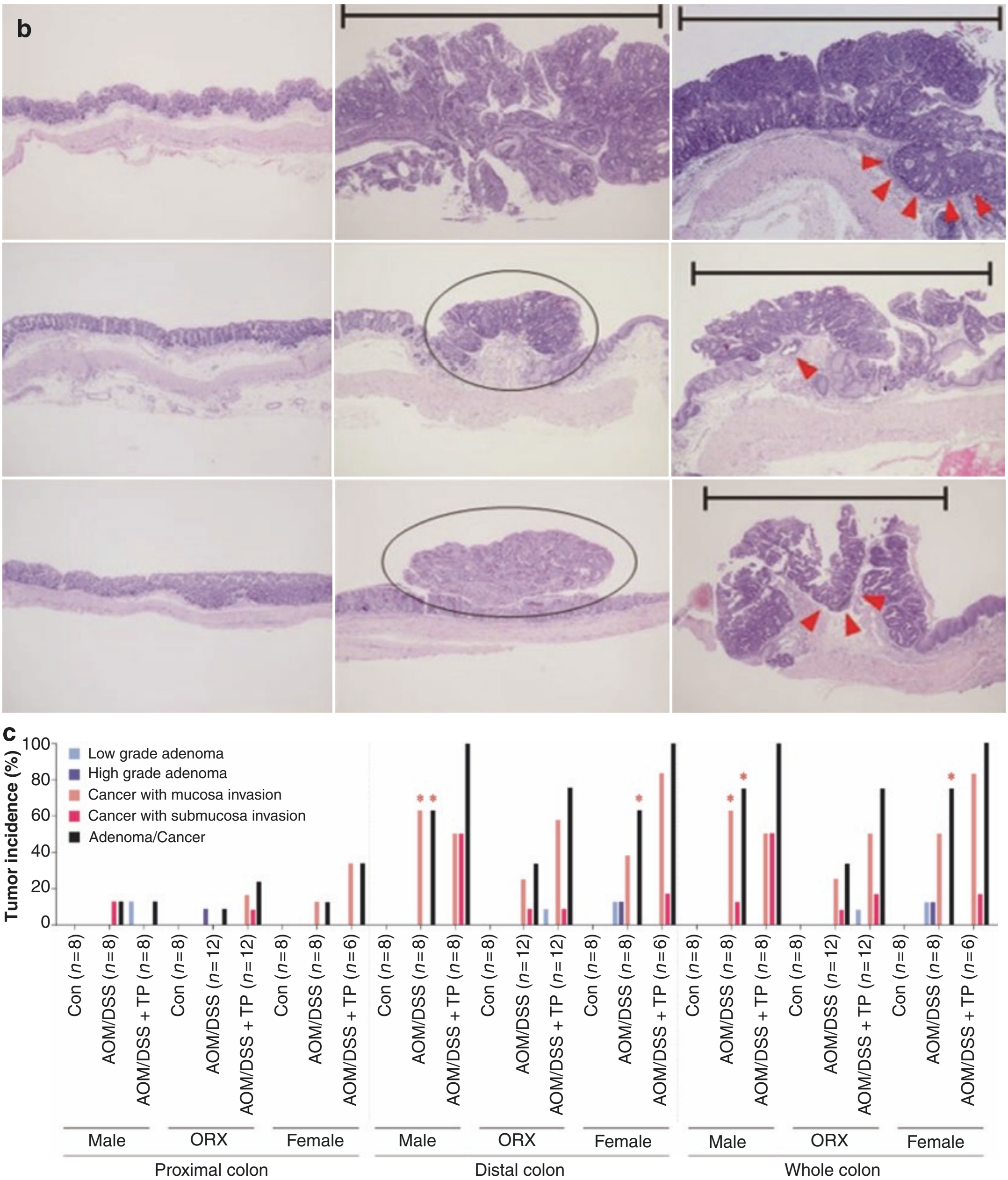

Fig. 20.14 (continued)

exogenous testosterone presented a stimulating effect on AOM/DSS-induced colitis and carcinogenicity [17]. However, key pathogenic mechanism has not been clarified why testosterone causes this specific CRC. In-depth mechanistic studies are needed to investigate the severity of colitis and CRC progression based on the anatomical distribution of the colon in ORX male mice.

20.3.2 Gut Microbiome

The gut microbiome is located in close proximity to the colorectal epithelium and there is cross interaction. Human intestinal microbiota is composed of 10^{13} to 10^{14} microorganisms which is about the same order as the number of human cells, and their total mass is about 0.2 kg [121].

Dysbiosis, a state of pathological imbalance in the gut microbiome, contributes to colorectal neoplasm [122]. The development of CRC has been associated with an overall reduction in microbial diversity [123] and specific enrichment of individual bacteria such as *Fusobacterium nucleatum* [124] and loss of potentially protective bacteria such as *Roseburia* [125]. In addition, the metabolic factors of microbiota such as bile acid and butyrate affect colon carcinogenesis [126].

20.3.2.1 The Role Gut Microbiome and Its Metabolite in the Development of Colorectal Cancer

Several studies in animal models have reported that estrogen signaling can help to maintain microbiome diversity [4] and ovariectomy has led to microbial dysbiosis although this was affected by strain and diet [127]. Furthermore, dietary supplementation with the hormone estradiol has been shown to increase microbial diversity in healthy male mice and to impact the ratio of bacteria in the microbiome of a CRC-induced mouse model [128]. The potential protective effect of estrogen was examined in a recent study using the AOM/DSS mouse model of intestinal specific ERβ deletion in the colitis-induced CRC model, suggesting that ERβ expression influenced gut microbiome diversity and attenuated these diseases [129]. Similarly, another study showed a reduction in gut microbiota diversity with the development of CRC, which was exacerbated in the absence of ERβ [130]. We also observed a significant increase in the microbial diversity (Chao1 index) in females, males supplemented with E2, and males treated with AOM/DSS/E2 compared with normal males [128]. In AOM/DSS-treated male mice, E2 supplementation showed significantly lower level of the Firmicutes/Bacteroidetes (F/B) ratio [128]. In addition, the ratio of commensal bacteria to opportunistic pathogens was higher in females and E2-treated males compared to normal males and females subjected to ovarectomy [128]. Our findings suggested that estrogen alters the gut microbiota in ICR (CrljOri:CD1) mice, particularly AOM/DSS-treated males, by decreasing the F/B ratio and changing Shannon and Simpson index [128]. This highlights a possibility that estrogen could cause changes in the gut microbiota, thereby reducing the risk of developing CRC [128].

20.3.2.2 Gut Microbiome Metabolite and Colorectal Cancer

Metabolic property of gut bacterial population has been investigated in relation to tumorigenesis. The well-known factor is short-chain fatty acids (SCFAs), nitroso compunds (NOCs), heme, and secondary bile acids [126] (Fig. 20.15).

20.3.2.2.1 Butyrate

The SCFAs, namely acetate, butyrate, and propionate, are quantitatively and metabolically the most important microbial end-products of the human colon fermentation process [131, 132]. Among them, butyrate produced by fermentation of dietary fiber is considered to be the main reason for the health benefit from the indigestible carbohydrate [133]. Butyrate is the preferred energy source for the colonic mucosa, and it suppresses the growth of tumor cells. The most investigated mechanism is that butyrate inhibits histone deacetylases (HDAC) and thus results in inactivation of many oncogenic signaling pathways [134]. The metabolic rearrangement in cancerous colonocytes is an appropriate means for providing biomaterials as well as energy that are essential for growth (Warburg effect). The effect of butyrate has been reported to differ according to dosage. Lower doses of butyrate have a differential effect on cell proliferation depending on the Warburg effect, while higher doses of butyrate was shown to inhibit proliferation regardless of the Warburg effect [135]. Butyrate is metabolized to acetyl-CoA; the dose of butyrate determines the utilization of epigenetic mechanisms [135]. A high dose of butyrate (5 mM) is a potent HDAC inhibitor, while at low doses such as 0.5 mM, butyrate might induce histone acetylation by an alternative mechanism that is distinct from its role as an HDAC inhibitor [135]. Butyrate induces cell differentiation, promotes cell apoptosis, and reduces tumor cell invasiveness [136]. Human study revealed that high red meat consumption increased the levels of pro-oncogenic microRNA including miR17–92 cluster in rectal biopsies, and increased butyrate supply through consumption of a butyrylated-resistant starch restored the miR17–92 miRNAs to

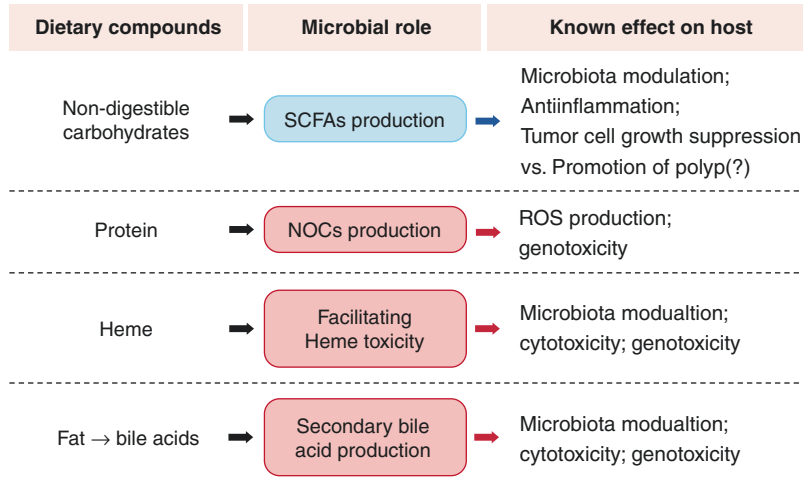

Fig. 20.15 Key microbiota metabolites which are related with colon cancer. *SCFAs* short-chain fatty acids, *NOCs* N-nitroso compunds, *ROS* reactive oxygen species (adapted from Yoon and Kim [126])

baseline levels [137]. Butyrate insufficiency may contribute to the development of inflammatory conditions because the acid has been shown to induce the differentiation of colonic T regulatory lymphocytes, which suppress inflammatory and allergic responses [138, 139]. Actually, butyrate was shown to suppress development of colon carcinogenesis in ApcMin/+ mice due to its Gpr109a agonist property through T regulatory cell differentiation [140].

Bifidobacteria are Gram-positive, anaerobic, saccharolytic bacteria belonging to the phylum Actinobacteria. Most butyrate producers in the human colon belong to the Firmicutes phylum and in particular *Clostridium* clusters IV and XIVa [131]. *Clostridium* clusters IV and XIVa butyrate producers are Gram-positive, highly oxygen-sensitive, anaerobic, and saccharolytic bacteria. The two dominant bacterial species are *Faecalibacterium prausnitzii* (up to 14% of the total fecal microbiota, *Clostridium* cluster IV) and *Eubacterium rectale* (up to 13% of the total fecal microbiota, *Clostridium* cluster XIVa) [131, 141]. Pyrosequencing study revealed the difference in fecal microbial population patterns between CRC and healthy subjects [142]. Phylotypes closely related to *Bacteroides* were prevalent in the cancer patients, while the butyrate-producing *Faecalibacterium* and *Roseburia* were significantly less abundant [142]. Potentially pathogenic *Fusobacterium* and *Campylobacter* species were more abundant in CRC patients than in the controls [142]. A cross-sectional study measured the fecal samples from African Americans with a high risk of colon cancer and rural native Africans with a low risk for the disease [143]. Native Africans had significantly higher abundance in the butyrate-producing bacteria such as *F prausnitzii*, *Clostridium* clusters IV and XIVa, while *Bacteroides* was the dominant microbial composition of African Americans [143]. However, there is no research regarding the sex difference of microbiota in the patients with CRC, so far. Instead there was a age difference in this butyrate-producing gut microbiota. That is, when gut microbiota in cecal contents of 6-, 31-, and 74-week-old and 2-year-old male Fischer-344 rats (corresponding to 5, 30, 60, and 80-year-old humans in terms of age) were analyzed using 16S ribosomal RNA metagenome sequencing major bacterial taxa changed in 31-week-old rats [144]. Especially, Lachnospiraceae, a SCFAs-producing family, increased at this age and unknown species EU622775_s and EU622773_s showed strong relationship with cecal butyrate level at 31 weeks of age, suggesting that butyrate production is different during lifespan with a peak in the middle age in rat [144]. Although SCFAs including butyrate have been generally shown to be beneficial, several challenging reports also exist. Several key studies on the relationship between butyrate, microbiota, and colon cancer are summarized in Table 20.1 [126, 138, 139, 141, 145–

151]. Higher fecal SCFA concentration correlated positively with metabolic syndrome risk factors such as adiposity, waist circumference, and homeostatic model assessment index, and inversely with high-density lipoprotein (HDL) [152]. In addition, significantly high concentrations of butyrate and propionate in obese children compared with normal-weight children were also reported [145]. Recently, direct instillation of sodium butyrate to represent the concentration of the SCFA in the distal part of the colon resulted in aberrant proliferation and transformation of colon epithelial cells in $APC^{Min/+}$MutS Homolog $2(MSH2)^{-/-}$ mice [148]. This discrepancy regarding the effect of butyrate on colon neoplasm could partly be attributed to the fiber itself that could play as a confounder [149]. Many studies testing the effect of butyrate on colon cancer development used dietary fiber as their source for butyrate production. However, the fiber may have independent effects from that of butyrate [149]. Dietary fiber can dilute possible carcinogens by increasing fecal bulk [150]. It also shortens time for proteolytic fermentation which may result in tumorigenic metabolites. Fiber could also bind carcinogens such as secondary bile acids [150]. Furthermore, many fibers contain health-promoting substances such as phytate and phytosterols [149]. In addition, the difference between in vitro vs. in vivo vs. human study can be another important factor explaining the discrepancy in the results [149]. Recently, a probiotic clinical trial proposed a "rebalancing" of butyrate concentration by administrating *L. paracasei* DG [151]. Interestingly, they found that the effect of the probiotic on the microbiota and SCFAs was associated with initial fecal butyrate concentration [151]. Specifically, objects with initial butyrate higher than 100 mmol/kg of wet feces showed reduction in butyrate and decrease in *Colostridales* genera. In contrast, for those with initial butyrate lower than 25 mmol/kg, the probiotic treatment increased butyrate concentration and decreased *Ruminococcus*. Based on the result, they suggested that fecal butyrate concentration may represent a biomarker to classify the

Table 20.1 Key studies on butyrate and microbiota regarding colon cancer (adapted from Yoon and Kim [126])

Author (year)	Study subject	Protocol	Effect of butyrate on colon
Whitehead et al. (1986) [145]	Cell line LIM1215	In vitro	Differentiating effect
Freeman (1986) [146]	Wistar rats	In vivo DMH	Enhancing the development of colonic neoplasia
Deschner et al. (1990) [147]	CF1 Mice	In vivo AOM	No difference in dysplasia or tumor
Archer et al. (1998) [148]	Cell line HT-29	In vitro	Growth inhibition
O'Keefe et al. (2009) [149]	Human	Cross-sectional	Higher fecal butyrate in Native Africans
Donohoe et al. (2011) [150]	C57BL/6 mice	Ex vivo CV vs. GF	Stimulating colon epithelial cell proliferation
Furusawa et al. (2013) [139]	Mice[a]	In vitro, in vivo	Inducing differentiation of colon Tregs
Belcheva et al. (2014) [151]	APCMin/+MSH2−/− mice[b]	In vivo	Inducing aberrant proliferation and transformation
Singh et al. (2014) [141]	Niacr1−/− mice[c]	In vivo, ex vivo AOM + DSS	Suppressing colon inflammation and carcinogenesis
Humphreys et al. (2014) [138]	Human	Randomized trial	Restoring oncogenic miRNA to baseline

DMH 1,2-dimethylhydrazine, *AOM* azoxymethane, *CV* conventional, *GF* germ-fre, *Tregs* regulatory T cells, *DSS* dextran sulfate sodium, *miRNA* microRNA

[a]GF IQI, C57BL/6 mice, Myd88−/−Ticam1−/− mice, OT-II transgenic mice

[b]C57BL/6J background

[c]C57BL/6 background

subjects who might benefit from the probiotic treatment [151].

20.3.2.2.2 Nitroso Compounds

N-nitroso compounds (NOCs) are known to exert highly carcinogenic effects following the formation of potent DNA alkylating agents during metabolism. The apparent total N-nitroso compound (ATNC) in food is generally non-detectable; the measurable fecal concentration of ATNC is suggested to be produced endogenously by N-nitrosation [153, 154]. Although most dietary nitrate and nitrite are absorbed in upper GI tract and excreted in the urine, people consuming a large amount of red meat can have nitrosating agents through colon [155].

Nitrate present in food and water is reduced by gut bacterial nitrate reductase to nitrite. Then nitrite reacts with nitrogenous compounds to produce NOC [154, 156]. Laboratory studies have shown that the bacterial strains belonging to *Escherichia, Pseudomonas, Proteus, Klebsiella, and Neissera* genera nitrosate the nitrogenous precursors [154, 155]. And the nitrate and nitrite reductase genes regulate the N-nitrosation activity [154]. Most of these microbiota belong to facultative anaerobes that can also use nitrate or nitrite for respiratory denitrification by reducing nitrate to nitrite, NO, N_2O, and N_2 [153]. ATNC investigated in germ-free and conventional microflora rats supports this concept, showing the ATNC in the stomach and large intestine of the conventional animals was formed by microbial action [157]. However, there is no research regarding the sex difference of NOCs in the patients with CRC, so far.

20.3.2.2.3 Heme

Heme iron is more abundant in red meat than white meat and fish, and they mediate transportation of nitrosating agents [155]. Dietary heme was also reported to alter the microflora by decreasing the number of gram-positive bacteria, leading to expansion of Gram-negative community [158, 159]. An animal study reported that mice fed with a diet supplemented with heme showed a damaged gut epithelium and hyperproliferation [160]. The damage and hyperproliferation was not observed in mice that received heme and antibiotics together, implying the role of microbiota in heme-induced epithelial hyperplasia [160]. In the study, antibiotics were shown to block heme-induced differential expression of oncogenes, tumor suppressors, and cell turnover genes, implying that antibiotic treatment prevented the heme-dependent cytotoxicity to the epithelium. The protective effect of antibiotics was attributed to elimination of sulfide-producing bacteria and mucin-degrading bacteria such as *Akkermansia*, because sulfide reduces disulfide bond to cause mucin denaturation [160]. A recent study also reported that dietary heme induces gut dysbiosis such as a decrease in α-diversity, a reduction of Firmicutes, and an increase of Proteobacteria, particularly Enterobacteriaceae [161]. The change was similar to DSS-induced colitis model. A reduction in fecal butyrate levels was also found in mice fed with the heme-supplemented diet, compared to the control mice [161]. Mice with heme-supplemented diet also showed a higher number of large adenomatous polyps than those with control diet [161]. However, there is no research regarding the sex difference of heme in the patients with CRC, so far.

20.3.2.2.4 Secondary Bile Acids

As bile acids are involved in the absorption of dietary fat in the intestine [162], high-fat diets induce an increase in bile secretion. Secondary bile acids are the metabolites produced by intestinal bacteria from primary bile acids (cholic and chenodeoxycholic acids). Large bowel anaerobic bacteria deconjugates and dehydroxylates, cleaving glycine and taurine residues to form the secondary bile acids such as deoxycholic acid and lithocholic acid [132, 154]. Metagenomic analysis showed that the microbial bile salt hydrolase activity is identified in all major bacterial divisions in the gut [163]. Bile salt hydrolase confers bile tolerance and hence improvement in survival of bacteria in murine intestine [163]. However, to the host, continuous exposure to the certain hydrophobic bile acids may induce oxidative DNA damage that might lead to tumorigenesis [162]. In serum and bile of patients with colonic adenomas, more deoxycholic acid was detected

than in healthy controls [164]. Secondary bile acids are toxic to several cell systems at physiological concentrations [164]. Direct installation of secondary bile acids in the large bowel can be tumor promoting. Infusion of deoxycholic acid led to damage of the mucosa, provoking increased cell proliferation [165]. Deoxycholic acid has been reported to cause resistance to apoptosis, as suggested from tissue specimens [166] and cell-line studies [167]. However, there is no research regarding the sex difference of secondary bile acids in the patients with CRC, so far.

20.3.3 Life Styles Including Diet, Physical Activity, Alcohol, and Smoking

Multiple lifestyle factors combine with biological sex differences to contribute to disparities between the sexes in many diseases including cancer [168]. Diet, exercise, and other lifestyle factors have been associated with CRC risk [169]. Recently, it has been observed that lifestyle factors such as diet and smoking could be linked with specific molecular CRC subtypes [170]. However, the impact of lifestyle factors on CRC risk seems to differ between men and women, implying an underlying biological contribution. That is, the European prospective investigation into cancer and nutrition study (EPIC) has reported that a high inflammatory profile (pro-inflammatory diet + sedentarism + obesity) showed a strong association with higher risk for CRC in men (HR 2.11; 95% CI, 1.50–2.97) and no significant association in women [171].

20.3.3.1 Diet, Physical Activity Levels, Obesity, Metabolic Syndrome, and Colorectal Cancer

20.3.3.1.1 Diet and CRC

Women have generally healthier dietary habits than men, with higher fiber and lower meat consumption, and less alcohol intake [4]. Interestingly studies have reported that dietary factors are associated differently with CRC depending on the location of tumors [5]. High carbohydrate intake increased right-sided colon cancer in women, but increased rectal cancer in men [172]. High fat and protein intakes increased risks of right- and left-sided colon cancers, respectively [173, 174]. Recent evidence from a large Canadian population–based case-control study suggested that high intake of polyunsaturated fat, trans-fat, cholesterol, sucrose, and lactose was associated with the increased risk of right-sided colon cancer [175]. In addition, meat consumption increased the risk of left-sided colon cancer compared to right-sided colon cancer [176–178], whereas total iron and iron from supplements were inversely associated with distal colon cancer [178]. Also, high calcium intake [179–181] and serum/plasma 25-hydroxyvitamin D level [182] were inversely associated with distal colon cancer. Consumption of soy products containing phytoestrogens has been shown to be inversely associated with the risk of CRC [183–186]. A recent meta-analysis found that soy consumption was associated with an approximately 21% reduction in CRC risk only in women, presumably due to the structural and metabolic similarities of soy isoflavones to estrogen [183]. This result supports a previous report suggesting soy consumption differentially affects estrogen metabolism depending on the endogenous estrogen level [187]. Indeed, an experimental study reported that high phytoestrogens intake increases ERα expression, decreases apoptosis, and induces inflammation markers in colonic mucosa of female mice possibly due to the high estrogenic background [188]. Thus, large population-based cohort studies need to report sex-specific estimates of dietary risk factors to provide better guidelines for cancer-preventive dietary intake.

20.3.3.1.2 Physical Activity Levels, Obesity, Metabolic Syndrome, and Colorectal Cancer

In spite of the wide variation in physical assessment methodology among studies, including type of activity (leisure-time or occupational) and method of assessment, prospective and retrospective studies support an inverse association between physical activity and risk of colon, but not rectal cancer [189]. In a prospective study of female nurses who were in the upper quintile of activity,

it was found that they were at almost half the risk of developing colon cancer compared to non-active women (relative risk [RR] 0.54; 95% CI, 0.33–0.90) [190]. This finding was supported by the Health Professionals Follow-up Study, a large prospective study of men [191]. Several biological mechanisms have been proposed for the inverse association between physical activity and colon cancer. First, a higher level of leisure-time activity was inversely related to the concentration of prostaglandin E2 (PGE2) in the rectal mucosa, suggesting a potential mechanism acting through PGE2 synthesis [192]. Prospective follow-up analyses of these data also show higher physical activity levels at baseline to be associated with lower PGE2 levels from biopsies taken 8–26 months later ($p = 0.01$). Second, hyperinsulinemia may also be an important mechanism through which physical activity exerts its protective effect [189]. High insulin levels are related to physical inactivity, high body mass, and central deposition of adipose tissue; furthermore, insulin is a mitogen for normal and neoplastic colonic epithelial cells [191]. In addition, recent studies have found diabetes mellitus to be a risk factor [193], and a prospective analysis of insulin's influence found a direct association with colon cancer risk [194]. However, this hyperinsulinemia partially explains the adiposity associated with CRC progression in postmenopausal women [195]. In addition, there was a report that the association between BMI and colon cancer in women is modified by menopausal status: a positive association was shown for pre-menopausal women but not among post-menopausal women [196]. Furthermore, higher BMI and lower physical activity levels have been positively associated with higher levels of circulating estrogens in post-menopausal women [197] suggesting that adipose tissue becomes an important source of estrogens in postmenopausal women and obese men. Taken together, the effect of obesity on colorectal neoplasia in pre-menopausal women acts via the insulin/insulin growth factor pathway while in post-menopausal women, higher levels of estrogens in obese women act in opposite directions to cancel out the effect of each other (i.e., BMI increases risk and estrogens lower risk) [189].

Regarding obesity and metabolic syndrome (MetS), we found the incidence of CRC with a sex difference. That is, when 408,931 Korean adults without cancer at baseline were followed up until 2013 (mean follow-up, 9 year), 5108 new cases of CRC occurred. Being underweight (18.5 kg/m^2) reduced the risk for CRC among women (adjusted HR 0.646; 95% CI, 0.484–0.863), whereas high BMI significantly increased the risk in men and in the elderly [198]. Obesity (≥25 kg/m^2), diabetes mellitus, and hypertension were identified as risk factors for CRC in men but not for women. Although metabolically unhealthy nonobese men had a higher risk for CRC than metabolically healthy nonobese men (adjusted HR 1.114; 95% CI, 1.004–1.236), the risk was lower than that in the obese men [198]. MetS and its components have been thought to be involved in the development of CRC and interestingly the effect was different depending on the gender and location of CRC. That is, when we evaluated the data of 22,809,722 Korean individuals of the National semi-compulsive cohort who underwent regular health check-ups between 2009 and 2012, the hazard ratio for CRC development in patients with MetS was 1.22 (95% CI, 1.20–1.24) and this association was more prominent in men than in women (HR 1.41; 95% CI, 1.37–1.44 vs. HR 1.23; 95% CI, 1.20–1.27, p for interaction <0.001) [199]. Left-sided colon cancers were more associated with MetS among men compared to women (HR 1.70; 95% CI, 1.61–1.80 vs. HR 1.43; 95% CI, 1.33–1.54), while right colon cancers showed a stronger association with MetS among women than men (HR 1.63; 95% CI, 1.49–1.78 vs. HR 1.34; 95% CI, 1.24–1.44) (all p for interaction <0.001, respectively) [199]. Having two MetS components was still associated with CRC development, and the association was the highest when two of glucose intolerance, abdominal obesity and low high-density lipoprotein cholesterol (HDL-C), combined [199].

20.3.3.2 Alcohol

Alcohol consumption is one of the most important known risk factors for human cancers [200]; and there is convincing evidence that alcohol consumption increases the risk of cancer in the col-

orectum, female breast, larynx, liver, esophagus, oral cavity, and pharynx [201]. Ethanol from alcoholic beverages is metabolized to acetaldehyde, which was classified as a human carcinogen by the IARC [202]. Ethanol itself can cause local irritation of the upper GI tract [203] and could stimulate carcinogenesis by inhibiting DNA methylation [204]. As sociological and cultural aspects of alcohol drinking vary by sex and that the toxic threshold of ethanol may differ by sex, it is important to provide specific summaries for women and men [204]. For instance, the risk of CRC by alcohol was 1.42 times higher in a Japanese cohort study [205]. When our team performed this study regarding the association between alcohol intake and CRC risk in a population-based prospective cohort of 23,323,730 adults who had undergone a biennial evaluation provided by the National Health Insurance Corporation between the years 2009 and 2012, 154,970 CRC cases were identified after median 5.4 years of follow-up [204]. Light drinking as well as moderate to heavy alcohol consumption significantly increased the risks of the CRC (HR 1.12; 95% CI, 1.11–1.14) compared with non-drinkers after adjusting for age, sex, smoking, exercise, income, BMI, and diabetes [204]. Light drinking including even one alcoholic drink a day (even less than 10 g per day) was associated with increased risks of CRC. It might be related with the variant allele of *ALDH2*, which breaks down acetaldehyde to acetate in the metabolism of alcohol, in Asians is much higher (28–45%) than in other ethnic groups [206]. However, the risks of the CRC increased with the amount of alcohol consumption but there was no significant increase in women. This finding was similar in the community-based study which was observed 6291 residents (aged 55 and older) of Ganghwa-do for 20.8 years from 1985 to 2005 in Korea [207]. In this study, the risk of CRC was 1.87 times higher in heavy drinkers than in non-drinkers [207]. In addition, the mortality associated with *soju* (Korean traditional alcohol with higher amount of ethanol) was significantly higher than that associated with *makgeolli* (Korean traditional alcohol with lower amount of ethanol) among men, but this difference was not significant among women [207]. Again the reason for this finding may be that the amount of consumption was larger and the duration of consumption was longer in men.

20.3.3.3 Smoking

A higher risk of adenomatous polyps has been consistently observed among smokers with relative risks ranging from 1.4 to 3.6 [189, 208], and an induction period of 30–40 years between smoking and risk of CRC has been proposed based on results from two large cohort studies [209, 210]. However, there are controversial results regarding smoking and CRC. That is, most of studies have reported positive associations between cigarette smoking and colorectal cancer [189], but several studies did not support an association [211, 212]. In addition, non-supportive studies were conducted in Sweden [210, 213, 214], which suggests some factor, possibly genetic, in Swedes may counter the impact of smoking [189]. The overall evidence supports the hypothesis that tobacco smoke is an initiator of colorectal carcinogenesis and the requirement for a very long induction period, possibly up to four decades, which suggests that studies assessing the role of tobacco exposure and CRC need to take into account this long induction period in their analyses [189]. In the latest and largest published study to date, based on data from the Cancer Prevention Study II (CPS II), 312,332 men and 469,019 women were followed prospectively from 1982 to 1996. The relative risk for CRC mortality was 1.32 (95% CI, 1.16–1.49) for women and 1.41 (95% CI, 1.26–1.58) for men who reported being current smokers [187, 215]. Of interest, cigar or pipe smokers who smoked for 20 years or more were also at increased risk of dying from CRC (OR 1.34; 95% CI, 1.11–1.62). A follow-up review continues to support the adverse effect of tobacco on the risk of CRC [216]. However, there is no data regarding the sex/gender difference of smoking effect on the CRC.

20.4 Colorectal Cancer Screening and Bowel Preparation

Socio-cultural barriers within women sometimes delay screening and diagnosis of CRC. In addition,

the length of colon is known to be longer in females than in males and the morphology of colon cancer is different between males and females. Bowel preparation for colonoscopy should be well performed in the left-sided colon cancer, especially sessile and lateral spreading tumor (Fig. 19.8a, b).

20.4.1 Colorectal Cancer Screening

Gender differences in CRC screening have been noted with women tending to consider CRC as a male disease and taking time to choose women gastroenterologists [217], whereas men tend to undergo colonoscopy right away more than women [218]. Non-invasive fecal occult-blood tests and colonoscopies are the gold standard for CRC screening as they facilitate early detection of asymptomatic CRC and the removal of adenomas [219]. Five-year survival rates for early stage CRC are close to 90%, whereas survival rates drop to 15% at advanced stage CRC. Population screening strategies established by developed countries have had a major survival benefit by detecting a higher proportion of localized, early stage malignancies [4]. In many developed countries, a population screening program has been established to screen the high risk population. However, the stating age is different in each country. That is, Irish program screens every man and woman aged 60–69 years old for a home fecal immunochemical test (FIT) every 2 years [220]. In Germany, screening starts with fecal occult blood test (FOBT) and colonoscopy starts at 55 years old which contributed to the early detection of CRC and longer survival rate. In Korea FOBT and colonoscopy starts at 50 years in the average risk population. As capacity grows, many countries are expanding their programs to make screening available for all the population from 55 to 79 years old. Younger adults with increased risk for CRC due to family history or a genetic condition are eligible for regular colonoscopies.

20.4.2 Bowel Preparation

CRC developed from right-sided or left-sided colon shows differences in incidence according to geographic region, age, and sex [35, 221]. It is known that patients with left-sided colon cancer are older and having more women than those with right-sided cancer. In addition, there is a difference in cancer morphology. That is, right-colon tumors are more often flat (Figs. 20.7a and 20.7b) while left-sided colon tumors have a polypoid-type (Figs. 20.7c and 20.7d) which can be more easily detected by colonoscopy [39]. Tumor location and prognosis of CRC are also different between men and women. However, studies that consider sex/gender-specific design and interpretation of CRC are insufficient. Colonoscopy is important for screening and diagnosis of CRC [222]. As inadequate bowel preparation affects the effectiveness and accuracy of colonoscopy examination bowel, preparation and colonoscopy quality management are important [222]. Several studies have reported that age, sex/gender, physical activity, and disease are associated with bowel preparation [223]. The length of colon is known to be longer in females than in males [224]. There have been some reports regarding sex difference in colonoscopy quality. They showed that male sex (OR 0.85) was associated with inadequate bowel preparation [225] and that men gender was a predictor of inadequate cleansing at right colon and left colon ($p = 0.040$ and $p = 0.014$, respectively) [226]. In terms of cecal intubation time that men were associated with prolonged cecal intubation time (913.86 ± 453.28 s in males vs. 910.44 ± 513.33 s in females, $p = 0.443$) [227]. In contrast, males showed a higher success rate of cecal intubation within 20 min than females (83.9% in males vs. 77.6% in females, $p = 0.004$) [228]. Our team also performed a research in the study group comprising a total of 12,561 patients (6148 females and 6413 males) under the hypothesis that there are sex differences in colonoscopy preparation quality, cecal intubation time, and withdrawal time (from point of cecal intubation to final withdrawal) [222]. Females showed better bowel preparation than males (mean total score of Boston bowel preparation score (BBPS): 7.4 ± 1.8 vs. 7.2 ± 1.9, $p = 0.001$) [222]. There was no significant difference in cecal intubation rate between males and females (95.2% in males vs. 95.4% in females, $p = 0.512$) but cecal intubation time was significantly longer in females

(male, 6.2 ± 6.1 min vs. female, 8.3 ± 6.4 min; $p < 0.001$) [222]. In contrast, withdrawal time was significantly longer in males (7.9 ± 3.5 min in males vs. 7.4 ± 3.1 min in females, $p < 0.001$), which was caused by the higher rate of colonoscopy biopsy in males ($p < 0.001$) and higher polyp detection rate in males (32.1% vs. 20.8%; $p < 0.001$ [222]. In addition, the number of cases with 3 or more polyps was higher in males ($p < 0.001$) and diverticulum was also more frequently detected in males (9.5% vs. 6.1%; $p < 0.001$) [222]. Our results suggest that different indication of colonoscopy and colonoscopy follow-up interval might be needed based on sex difference of bowel preparation method and colonoscopy withdrawal time.

20.5 Conclusions

Clinical and preclinical studies have indicated that there are sex/gender-associated differences in CRC development. Women have a higher risk of developing right-sided (proximal) colon cancer than men, which is associated with more aggressive form of neoplasia compared to left-sided (distal) colon cancer. Both genetic and environmental factors play roles in sex/gender differences in right- *vs* left-sided colon cancers. Therefore, biological and pathophysiological differences in CRC development between men and women need to be clearly addressed. Sex hormones contribute to CRC risk, but this is modulated by lifestyle and environmental factors. For instance, AOM/DSS-induced colon cancer mouse model showed that the CRC incidence was definitely higher in male than female mouse and the treatment of 17β-estradiol during the DSS inflammation period prevented the development of CRC [15]. Endogenous estrogen in females protects against the development of left-sided colon cancer, and exogenous E2 replacement in ovariectomy female mice showed protective effects against AOM/DSS-induced colitis and carcinogenesis. In addition, endogenous and exogenous testosterone presented a stimulating effect on AOM/DSS-induced colitis and carcinogenicity. In addition to the sex hormones diet, exercise and other lifestyle factors have been associated with CRC risk. In addition, it has been observed that lifestyle factors such as diet and smoking could be linked with specific molecular CRC subtypes. However, the impact of lifestyle factors on CRC risk seems to differ between men and women implying an underlying biological contribution. Socio-cultural barriers within women sometimes delay screening and diagnosis of CRC. Bowel preparation for colonoscopy should be well performed in the left-sided colon cancer, especially sessile and lateral spreading tumor. Given the biological and socio-cultural differences between genders, gender-specific analyses should be conducted to provide optimal cancer prevention strategies and to reduce the number of new CRC cases both in men and women.

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Part IX

Gut-Microbiome-Brain Axis

Gut-Microbiome-Brain Axis

21

Nayoung Kim

21.1 Introduction

Disorders in gastrointestinal (GI) motility, visceral hypersensitivity, infection, inflammation, and changes in the gut microbiota are hypothesized to be important mechanisms of the pathophysiology of functional gastrointestinal disorders (FGIDs), such as functional dyspepsia (FD) and irritable bowel syndrome (IBS). Recent research has actively explored the interactions between the central nervous system (CNS), GI system, and gut microbiota; and the biopsychosocial model (Fig. 21.1) suggests that GI symptoms occur as a result of the interaction among sensation disorders, changes in motility, combined activation of the autonomic nervous system (ANS) and CNS, and the gut microbiota [1]. In the past, the term "brain-gut axis" was used to refer to the interaction between the areas in the CNS responsible for emotion or cognition and the areas involved with functions within the GI tract such as sensation and motility. However, as the importance of the gut microbiota has been recognized, it has been referred to as the "brain-gut-microbiome axis" or "the gut-microbiome-brain axis" [2] (Fig. 21.2). Many pre-clinical and clinical trials have demonstrated the bidirectional interrelationships among the CNS, GI system, and gut microbiota. These gut microbiota were found to be in close contact with the CNS through the neural, endocrine, and immune signaling systems. The brain modulates the expression of genes in the gut microbiota by controlling GI secretion and motility, intestinal permeability, and hormone secretion and the ANS [3]. Various changes that occur in the CNS or the GI tract influence each other, rather than occurring separately. These three elements function as components of a biological system, and when a problem occurs in any part of this process, this problem affects the entire system, causing IBS, obesity, and psychological/neurological diseases [3]. In fact, external stimuli (e.g., vision and scent) and changes that occur in the CNS (e.g., emotion and cognition) can influence the function of the GI tract, such as sensation, motility, inflammation, and secretion; and various stimuli that occur within the GI tract can impact pain recognition, mood, and behaviors in the CNS. FGIDs can change depending on dysbiosis. Based on the fact that FGIDs are more common in females [4] (Table 21.1), it can be inferred that there are sex/gender differences in this brain-gut-microbiome axis. In order to understand the role of brain-gut interactions in FGIDs, recent research has actively explored functional or structural changes in the CNS through the assessment of neuroimaging for visceral pain and changes in endocrine responses or intestinal immune responses that occur due to

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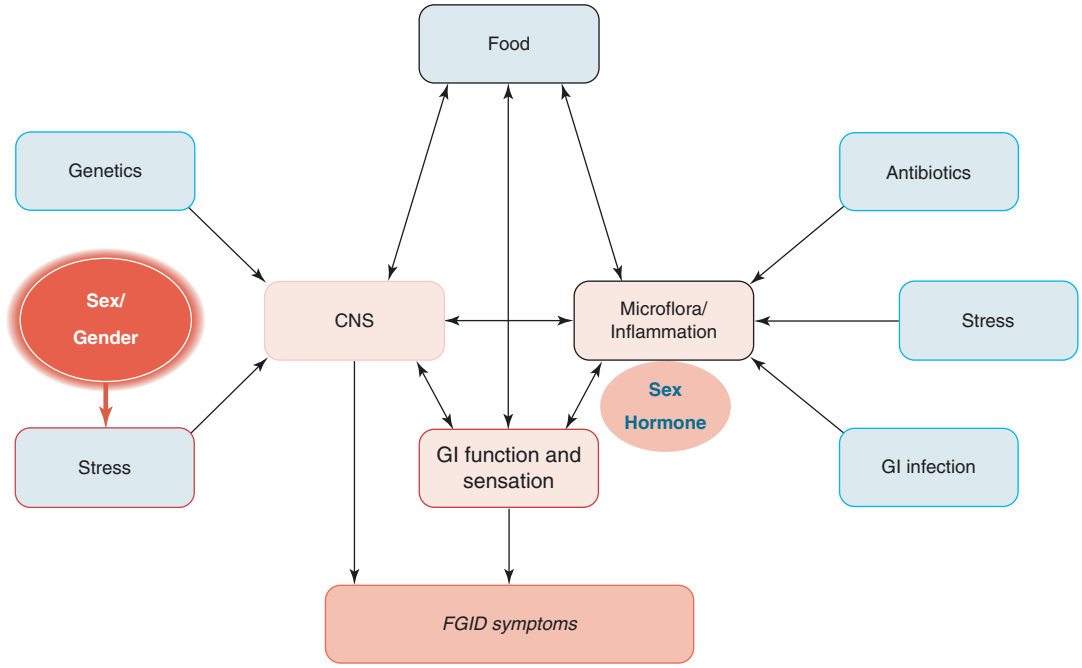

Fig. 21.1 Biopsychosocial model of functional gastrointestinal disorders. *CNS* central nervous system, *ENS* enteric nervous system (modified from Chey [1])

various stimuli in the CNS. With the use of next-generation sequencing (NGS) in the analysis of the gut microbiome, many studies are being published. However, it is very difficult to find studies which analyzed sex/gender differences and it could be due to the small number of participating subjects. In addition, another reason could be that women account for most participants in these clinical trials.

21.2 Sex/Gender Differences in the Brain Areas Related to Functional Gastrointestinal Disorders

It is very common for psychological disorders such as depression and anxiety to co-occur with FGIDs. In addition, there are sex/gender differences in responses to stress hormones. Various explanations have been proposed regarding why females are more vulnerable to stress responses than males. One mechanism is that females are more sensitive to the locus coeruleus-norepinephrine system, which increases sensitivity to corticotropin-releasing factor (CRF) and stress [5]. In contrast, when CRF is over-secreted in males, CRF receptors are internalized into cells; thus, the response to CRF is dulled. This internalization process does not occur in females, and stress is thereby delivered throughout the entire body [5]. In addition, estrogen blocks the negative feedback of cortisol by acting on the estrogen alpha receptors in the hypothalamus, which impacts stress vulnerability in females [5]. When females are exposed to severe and constant stress, they experience more severe effects because the CRF-related endocrine system and arousal system are not regulated [5], leading to the occurrence of somatization disorders, which are common in severe cases of FGIDs [5]. Other than the relationship with CRF, there are sex/gender differences in the functional linkages in the amygdala, which oversees postprandial satiety, food consumption, emotional regulation, and endogenous pain inhibition. It has also been discovered that in patients with FGIDs, there are functional or structural differences in the default

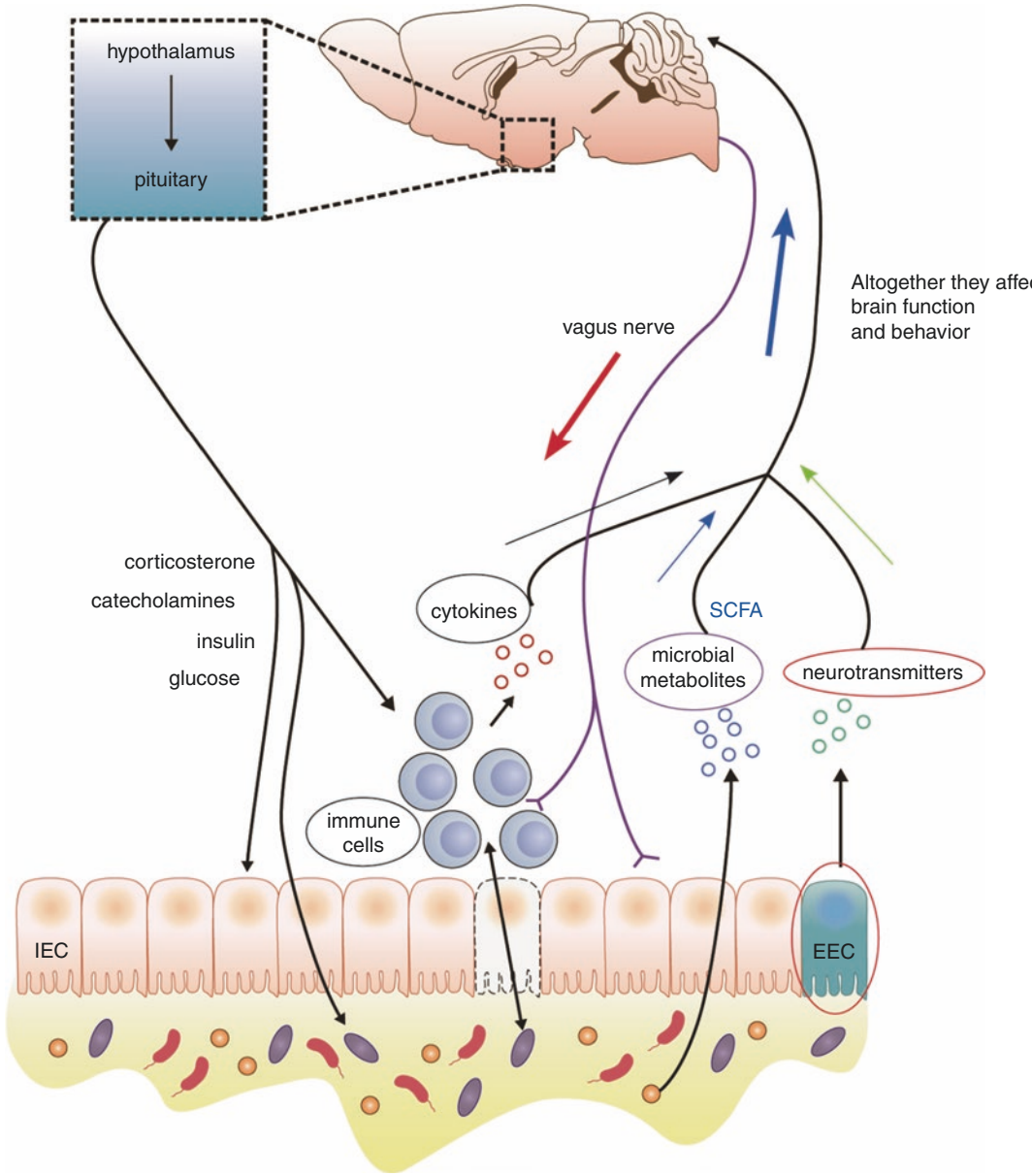

Fig. 21.2 Bidirectional gut-microbiome-brain signaling system. The gut and the brain maintain bodily functions after receiving direct or indirect signals through the immune, neural, endocrine, and metabolic pathways. With the intestinal epithelial cells (IECs) as the foundation, microbes secrete short-chain fatty acids (SCFAs) or chemotactic peptides to impact the brain or combine with receptors in enteroendocrine cells (EECs) to secrete peptides such as signaling substances. Moreover, microbes influence intestinal immune cells and change cytokines to influence the brain or modify behavior. When the neural pathways are activated through these pathways, they influence the secretion of cytokines in the intestines through the secretion of hormones or other peptides (adapted from Jašarevic et al. [2])

mode network and salience network in brain areas depending on sex/gender [6–9]. Of particular note, in female patients with FD, severe disorders in cognitive-affective processing in the amygdala were reported [6]. When the neuroimaging findings of the basolateral area of amyg-

Table 21.1 Differences the in incidence of FGIDs by sex/gender (adapted from Houghton et al. [4])

FGID	Effect of sex
Esophageal	
Globus	F > M
Rumination	F = M F > M
Functional chest pain	F = M F > M (at tertiary care)
Functional heartburn	F = M
Dysphagia	F > M
Gastroduodenal	
Dyspepsia	F = M
Aerophagia	M > F F > M
Functional vomiting Biliary tract	F = M F > M
Lower GI tract	
IBS	F > M
Functional constipation	F > M
Functional diarrhea	M > F
Functional bloating	Discordant F > M
FAPS	F > M
Fecal incontinence	F > M (at home) M > F (nursing homes)
Functional anorectal pain	F > M
Outlet delay	F > M

FAPS functional abdominal pain syndrome, *GI* gastrointestinal

dala (BLA) were compared between female patients with FD and female controls as well as male patients with FD, resting-state functional connectivity (rsFC) in the insula was found to be higher in female patients with FD, and the rsFC of the medial prefrontal cortex and the lateral and dorsal lateral prefrontal cortex was lower [6]. These results help to explain why females are more sensitive to pain and report digestive pain/discomfort more frequently, as visceral afferent circuits are activated and negative emotions are increased in female patients with FD [6].

21.3 The Role of the Microbiome in the Gut-Microbiome-Brain Axis

Animal studies were the first to report the role of the gut microbiome in stress responses. Mice that did not have a normal gut microbiome when they were young did not have normal stress responses after they matured, but when at least one strain of bacteria was injected when they were young, abnormal stress responses were partially normalized [10]. Mice without normal gut microbiome when they were young had low brain-derived neurotrophic factor (BDNF) levels in the brain cortex and the hippocampus [10, 11] and low expression levels of serotonin (5-HT) receptors 1A and 1B in the hippocampus [11], suggesting that the gut microbiome affects the CNS. Other than responses to stress, studies have reported responses to anxiety [11, 12], behaviors related to stress [13–15], and nociceptive responses [16, 17]. When a broad-spectrum antibiotic was used, changes in the gut microbiome were found to be accompanied by an anxiety response similar to that in aseptic mice [18]. Anxiety-related behaviors decreased when mice were fed probiotics [13, 19, 20], which indicates the impact of the gut microbiome on the brain [3]. The effect of the gut microbiome on the brain is known to be related to neuroimmune mechanisms concerning the vagus nerve and neuroendocrine mechanisms [2, 13, 21] (Fig. 21.2). This communication is related to the short-chain fatty acids (SCFAs) that are secreted from the gut microbiome, secondary bile acids, and tryptophan metabolites [21–23]. These SCFAs primarily deliver signals to the brain through the effects of enteroendocrine cells (EECs), enterochromaffin cells (ECCs), and the mucosal immune system; however, they are also hypothesized to enter the bloodstream or cross the blood-brain barrier from time to time [2, 22, 24, 25] (Fig. 21.2). Based on studies regarding the relationship between the microbiome-brain-gut axis and sex hormones, sex hormones participate in the central and peripheral control mechanisms of the pathophysiology of IBS; influence the stress response, visceral hypersensitivity, motility, intestinal barrier function, and intestinal mucosal immune function; and simultaneously have a direct impact on the gut microbiome [4] (Fig. 21.3). Estrogen, in particular, controls the gut microbiome, which affects the metabolism of estrogen [26], lead-

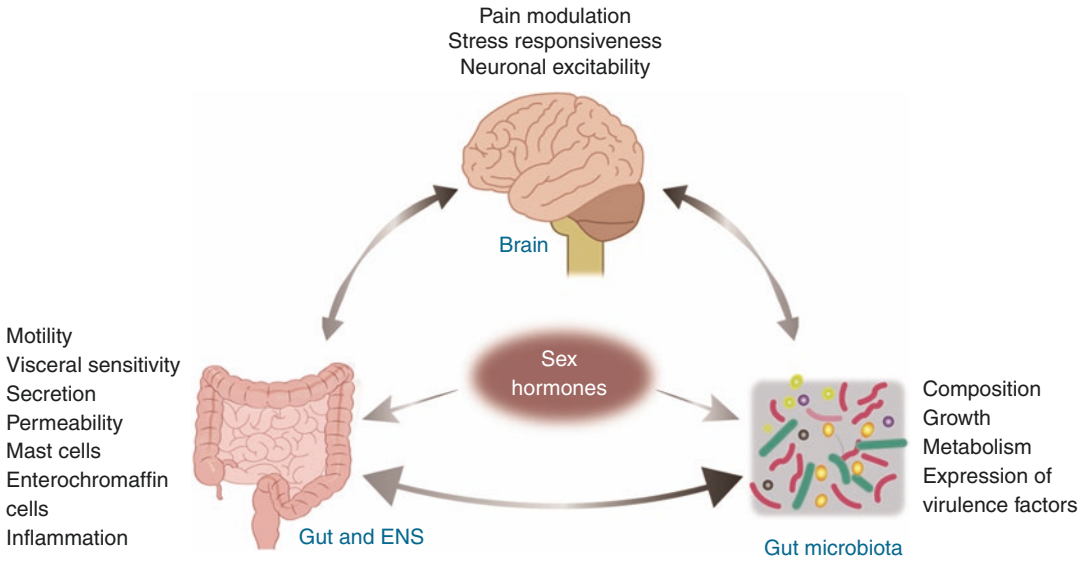

Fig. 21.3 Interrelationship between sex hormones and the brain-gut-microbiome. Sex hormones participate in the central and peripheral control mechanisms of the pathophysiology of irritable bowel syndrome; influence stress response, visceral hypersensitivity, motility, intestinal barrier function, and intestinal mucosal immune function; and simultaneously have a direct impact on the gut microbiome (adapted from Houghton et al. [4])

ing to the suggestion of the term "microgenderome" [27].

21.4 Pathophysiology of Functional Gastrointestinal Disorders in Terms of Gut-Microbiome-Brain Axis Depending on Sex/Gender

Visceral hypersensitivity, disorders in GI motility, intestinal permeability, infection, inflammation, and changes in the gut microbiota are hypothesized to be important pathophysiology of FGIDs such as gastroesophageal reflux disease (GERD), FD, and IBS. Non-clinical and clinical evidences regarding the sex/gender differences in pathophysiology could be summarized and presented as follows.

21.4.1 Visceral Pain Perception

In the baseline status without stress, females show a greater response to visceral pain than males [28, 29]. It is known that genetic factors influence these baseline differences [30]. Visceral pain is related to chemical stimuli, inflammation, and stress. Stress, especially repeated stress and stress in childhood, causes visceral hypersensitivity in females [31]. Such visceral hypersensitivity was found to cause a large response in female rodents days and even months after the stressor [32, 33]. There are many arguments about the role of female sex hormones, but it is difficult to study this topic in rodents as their menstrual cycle is very short. In human studies, females report abdominal pain related to bowel movements. Female patients with IBS mainly report constipation, excessive strain, and bloating, while male patients with IBS report symptoms related to diarrhea such as an increase in the frequency of bowel movements [34]. No definitive conclusions have yet been reached on the effect of sex/gender on visceral pain in healthy individuals and patients with FGIDs [35–39], but it is known that female patients with IBS have higher sensitivity toward repeated pressure in the sigmoid colon than male patients [38, 40]. The reasons for different results across studies may include differences in study design, small sample size, ovarian hormones and their receptors, stress level and mood, childhood experiences, and social factors.

21.4.2 Disorders in Gastrointestinal Motility and Intestinal Permeability

Estrogen and progesterone influence disorders in GI motility and intestinal permeability [41]. An example is decreased intestinal movement when estrogen and progesterone are injected after ovariectomy [42]. It is hypothesized that nerves involved in nitric oxide signaling in the myenteric plexus [43] and mast cells distributed in the GI tract are related [44]. Stress decreases upper GI motility and increases lower GI motility, especially in female animal models [45, 46], and it is known that this effect is mediated by corticotropin-releasing factor receptor-1 (CRFR-1), which is activated by estrogen and expressed in the intestinal myenteric plexus [47]. Sex/gender differences in the digestive organs depend on the organ. For example, there are no sex/gender differences in the anatomy of the esophagus or esophageal nerve distribution, but there is a slight difference in function [48]. Meanwhile, females have slower gastric emptying than males, both for solid food and liquid food [49–53]. Postprandial gastric body relaxation is more delayed in females than in males, and perception scores are higher among females than males [54]. Intestinal transit time is generally faster in males than in females, and the transit time is especially slow in the right ascending colon for females [55–57]. Although not adjusted for the menstrual cycle, healthy females had lower contractility in 24-h ambulatory intestinal manometry than males [58]. Anal sphincter pressure, maximum contractility, and volume at the time of desire to defecate are lower among females [59, 60].

Estrogen also influences the expression of tight junction proteins in the intestinal barrier, which protect the host from harmful bacteria. The author's study team reported that expression of occludin (OCLN) increased in female patients with GERD [61] and that intestinal permeability decreases and expression of genes and proteins related to inflammation such as Krüppel-like factor 4 (KLF4), nuclear factor κB (NF-κB), inducible nitric oxide synthetase (iNOS), and cyclooxygenase-2 (COX-2) decreased due to increased expression of mucin 2 (MUC2), zonula occludens 1 (ZO-1), OCLN, and claudin 4 (CLDN4) genes, when 17β-estradiol was administered in mice models in which colitis was induced using azoxymethane/dextran sulfate sodium [62]. These results are consistent with reduced inflammation from decreased expression of NF-κB and COX-2 and increased expression of heme oxygenase-1 (HO-1) and NAD(P)H-quinine oxidoreductase-1 (NQO1), which are antioxidant enzymes, when 17β-estradiol was given to CCD841CoN, a normal female intestinal epithelial cell line [63].

21.4.3 Sex Difference of Central Processing of Visceral Stimuli

Specific area in the brain is activated as a response to a specific stimulus, metabolic activity, and the amount of blood flow increase. When single-photon emission tomography (SPECT), positron emission tomography (PET), or functional magnetic resonance imaging (fMRI) is used, the level of neuron activity can be assessed by measuring the amount of blood flow in a certain brain area. Whereas it takes several minutes for changes in blood flow to be reflected in PET images, fMRI can measure changes within seconds, and the image is clear without having to use isotopes. fMRI is therefore used in many studies about sensory functions and sensory areas in the brain [64]. These diagnostic methods can confirm the mechanism by which GI sensation and motility are controlled in the CNS and the area responsible for the emotion or recognition caused by responses to specific stimuli [65]. When healthy controls and patients with IBS were compared through brain imaging studies, there were disorders in the sensory processing of the central nerves regarding visceral pain [66]. In fMRI images, there were differences in the signaling system by sex/gender even in healthy controls, and in patients with IBS, sex/gender differences were observed [4]. Stimuli that expand the rectum increase the activation of the anterior cingulate cortex in patients with IBS [67], and several studies utilizing fMRI and PET reported that

anterior cingulate cortex activation was significantly higher in patients with IBS than in controls [64, 68–71], suggesting that the anterior cingulate cortex is responsible for recognizing early pain stimuli in patients with IBS [66]. An increase in anterior cingulate cortex activation was related to anxiety, stress, maladaptive coping, and history of abuse [72]; and patients with IBS who have a history of abuse feel a significantly higher level of pain for the same rectal stimuli and have significantly increased activation in the dorsal posterior cingulate cortex and dorsal middle cingulate cortex [73]. There can be sex/gender differences in the level of activation in certain areas observed on brain imaging. For the same rectal stimulus, activity in the ventromedial prefrontal cortex, right anterior cingulate cortex, and the amygdala increased among females, while activity in the dorsolateral prefrontal cortex, insula, dorsal pons, and periaqueductal gray increased among males [74]. This result indicates that regarding information processing related to visceral stimuli, females use areas related to emotions and autonomic regions more, while males use the corticolimbic pain inhibition system more [4]. When examined using connectivity modeling, these sex/gender differences were hypothesized to reflect differences in the effective connectivity of the emotional arousal circuitry rather than differences in the visceral afferent processing circuitry [4, 41] (Fig. 21.4). A recent study found sex/gender differences in brain activation/connectivity even without stimuli such as rectal expansion, and the insula was more highly activated in female patients with IBS than in males [75]. Oscillatory dynamics in the amygdala and the hippocampus, which are responsible for emotions, were increased due to the increase in high-frequency power in female patients [75]. This finding was interpreted as showing the tendency to rely on the process of perception among males and the tendency to rely on interoceptive awareness among females. The effect of early adverse life events (EALs) on resting brain con-

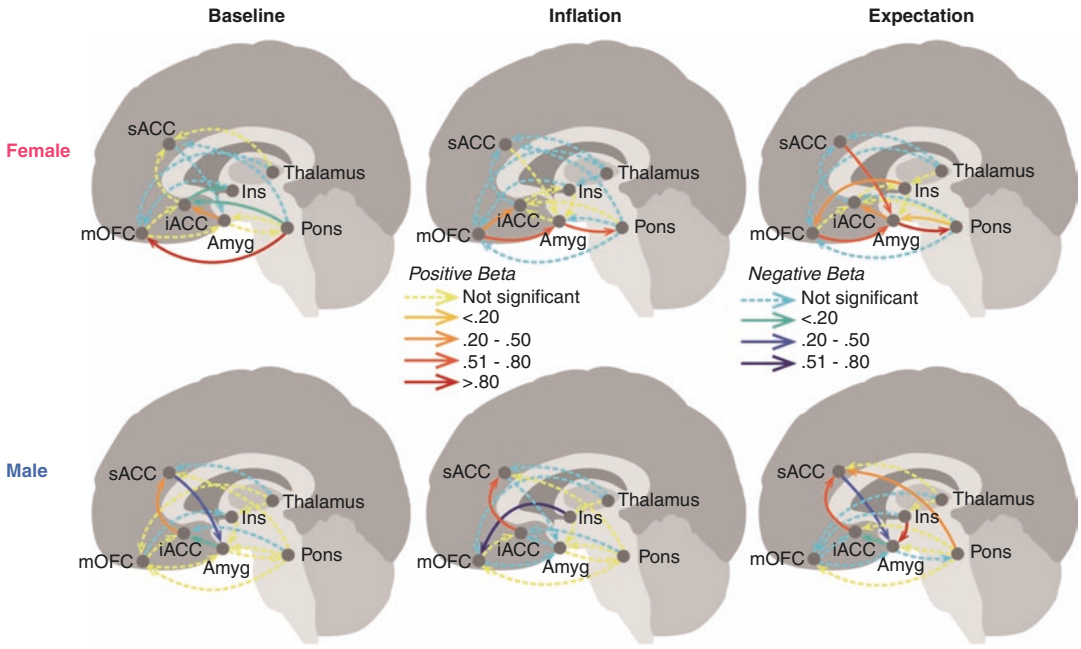

Fig. 21.4 Baseline, anal inflation, and pain expectation by sex/gender. Schematics of homeostatic-afferent, emotional-arousal, and cortical-modulatory circuits in three periods. The β coefficients that indicate effective connectivity are shown using line thickness and color. Solid lines are significantly different from zero, but dotted lines are not significant. *Amyg* amygdala, *INS* insula, *mOFC* medial orbital frontal cortex, *sACC* supragenual anterior cingulate cortex (adapted from Houghton et al. [4])

nectivity among patients with IBS was observed [76]. EAL scores were associated with the increased connectivity in thalamus, insula, middle temporal gyrus, and cerebellum networks; but this phenomenon was only observed in males [4]. The right subgenual anterior cingulate cortex was found to be thinner in female patients with IBS than in male patients [77]. The integrity of the sensorimotor and descending pain modulation pathways was weaker in female patients than in male patients, and this difference was not observed in healthy individuals [78]. In summary, both functional and structural changes of the brain occur in patients with IBS, and the level and duration of pain are related to structural changes [79].

21.4.4 Stress and the Neuroendocrine Response

Stress is considered a type of physiological adaptive response and can be defined as an abrupt or imbalanced status that threatens the individual's homeostasis. When stress increases too drastically and exceeds the adaptive capacity, it impacts various parts of the body [80]. Stress is an important component of the pathophysiology of FGIDs [81] and can cause inhibition of gastric emptying, increased intestinal motility, and visceral hypersensitivity. The CNS contains the emotional motor system, which is the core of stress response control, and the paraventricular nucleus in the hypothalamus, amygdala, and periaqueductal gray also participate in this process [82] (Fig. 21.5). When the emotional motor system is activated due to exteroceptive stress such as psychological stress and interoceptive stress such as intra-intestinal infection, motility disorder, and inflammation, the body attempts to control the stress through ANS responses, visceral sensation modulation, and neuroendocrine responses. ANS responses cause changes in intestinal motility and secretion, and the periaqueductal gray controls visceral sensation signaling and signals the pituitary to activate the hypothalamus-pituitary-adrenal (HPA) axis, influencing the physiology of the intestinal tract and the brain [82]. CRF is the hormone that plays the most important role in this process.

21.4.4.1 Corticotropin-Releasing Factor and Receptors

CRF is a protein composed of 41 amino acids that was first discovered in 1981 [83]. In response to physiological or psychological stress, CRF is secreted from the paraventricular nucleus in the hypothalamus and amygdala. CRF is the main neurohormone that activates the HPA axis and acts as the main neurotransmitter in the emotional, behavioral, and autonomic responses to stress [84–86]. The main target of CRF modulation is the locus coeruleus-norepinephrine system, which controls alertness in the stress response. The physiological responses and the secretion of mediators such as CRF were found to be significantly higher in patients with IBS than in healthy individuals in response to the same stress [87–89]. The myenteric plexus in the brain and GI tract and CRF receptors that exist in the intestinal mucosa are related to acute or chronic stress and act on various areas in the CNS and GI tract, acting as important mediators that cause changes in GI function [86, 90, 91]. There are two types of CRF receptors. Activation of CRF type 1 (CRF_1) increases intestinal motility, the inflammatory response in the intestinal mucosa, pain, and anxiety; and CRF type 2 (CRF_2) inhibits gastric emptying, reduces inflammatory responses and pain, and suppresses anxiety [92, 93]. However, CRF receptors do not influence changes in intestinal motility that occur without stress [81, 84].

21.4.4.2 The Role of CRF_1 in the Central Nervous System

In various animal models, when CRF is injected into the CNS, intestinal motility and defecation increase [94–96]. This response occurs through the CRF_1 receptors in the CNS. When drugs that selectively react to CRF_1 receptors, such as ovine CRF and r/h CRF, are injected into the CNS in animal studies, responses similar to the increase in intestinal motility caused by stress can be observed [97]. When CRF receptor antagonists or CRF_1 receptor-selective antagonists are

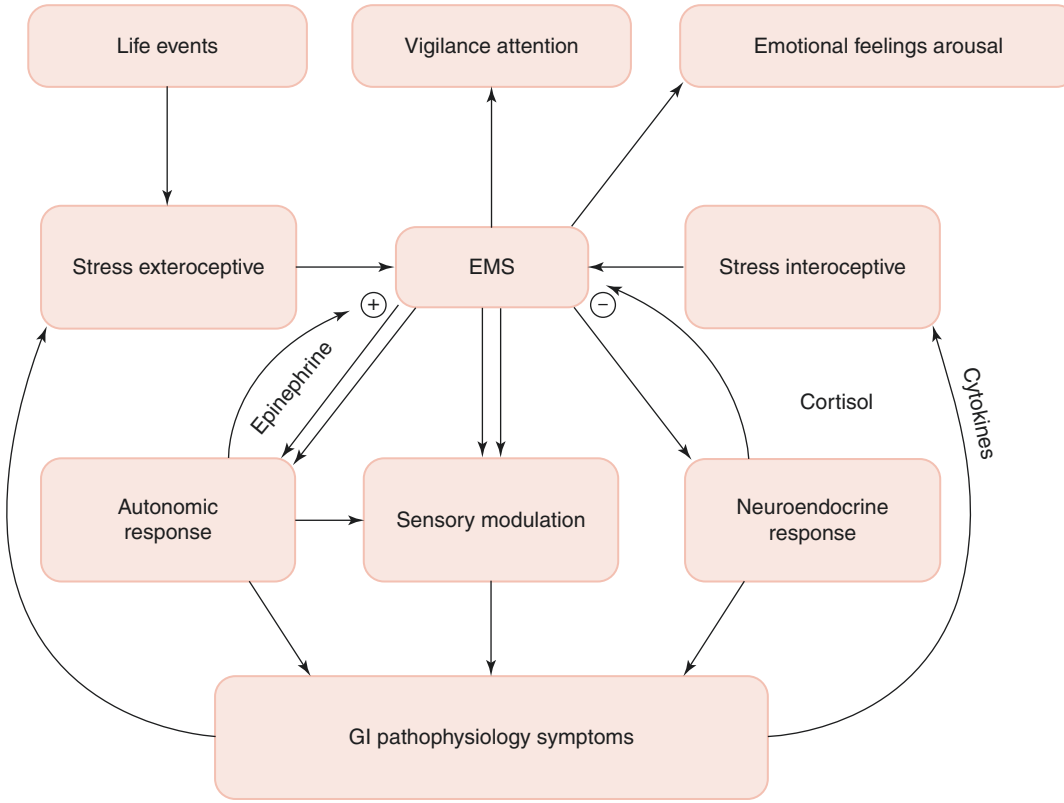

Fig. 21.5 The emotional motor system (EMS). The paraventricular nucleus in the hypothalamus, amygdala, and periaqueductal gray participate in this role. When the emotional motor system is activated due to exteroceptive stress such as psychological stress and interoceptive stress such as intra-intestinal infection, motility disorder, and inflammation, the body attempts to control the stress though autonomic nervous system responses, visceral sensation modulation, and neuroendocrine responses (adapted from Mayer et al. [82])

injected into the CNS, the increase in intestinal motility or defecation caused due to stress or the injection of CRF into the CNS is blocked [81, 94, 95, 98]. In contrast, when CRF_2 selective antagonists are injected into the CNS, the response of increased intestinal motility caused by CRF is not blocked [84], indicating that CRF_1 receptors play a major role in the stress-induced increase in intestinal motility. Changes in intestinal motility related to CRF in the CNS occur even when HPA axis activation is blocked [99] through the activation of parasympathetic nerves via the vagus nerve [96, 100]. In animal studies, when serotonin type 3 ($5\text{-}HT_3$) receptor antagonists and serotonin type 4 ($5\text{-}HT_4$) receptor antagonists are intravenously injected and CRF is injected into the CNS, the increase in defecation caused by CRF is blocked. However, this inhibitory effect does not occur when these formulations are injected into the CNS [101, 102], suggesting that the main pathway of CRF is the activation of various receptors in the GI tract through the vagus nerve [66].

21.4.4.3 Sex/Gender Differences in the Function of Hypothalamus CRF and the Signaling System of CRF_1 Receptors

Even without stress, the levels of HPA axis hormones such as glucocorticoid and corticosterone are higher in female rodents than in male rodents, and when they are stressed, the high levels are maintained for a longer time, as more adrenocorticotropic hormone (ACTH) and glucocorticoids are secreted [103, 104]. When female rodents are

not under stress, the increased expression of CRF in the paraventricular nucleus is proportional to the blood estrogen level [103, 104], and CRF expression has been found to increase in response to childhood or psychological stress [104, 105]. However, restraint stress and chronic mild stress caused increased expression of CRF mRNA in the paraventricular nucleus only in male rodents, which may have been due to the already high expression of CRF mRNA in females [103, 106–108]. In human studies, these results have not been clearly observed, which might be due to differences in the CRF response depending on the stressor. Summarizing the results of relevant research, females are more vulnerable to acute stress and are less able to adapt to chronic stress or high-CRF situations. One reason why females are vulnerable to mood and anxiety disorders is the high expression of CRF in females and the HPA axis. The explanation is becoming clearer due to advances in our understanding of the molecular biological mechanisms of β-arrestin-2 in relation to CRF receptors. β-arrestin-2 controls the effect of CRF_1 receptors using G-protein-independent signaling cascades such as mitogen-activated protein kinase (e.g., ERK2, JNK3, and p38), tyrosine kinases (e.g., c-SRC, Hck, Fgr, Yes), AKT, PI3 kinase, and RhoA through scaffolding signaling molecules [5, 109–112] (Fig. 21.6a). In contrast, β-arrestin-2 does not interact with CRF receptors in females, and these receptors instead comprise a signaling system different from that of males, depending on GTP-binding proteins (Gs) [5] (Fig. 21.6a). Depression in post-traumatic stress disorder (PTSD) clearly demonstrates this difference clearly. In order for pharmacological treatment to be effective in females, hyperarousal should be decreased by changing the pathway for CRF_1 receptor signaling from the Gs pathway to the β-arrestin-2-related pathway.

When CRF is secreted in stress situations, specific responses occur in the endocrine, behavioral, and ANS through the HPA axis and the locus coeruleus-norepinephrine system. In the acute phase, these responses allow individuals to respond well to emergency situations, but when the activation of CRF_1 is continued, mood disorders and depression are caused due to a lack of precise control of the HPA axis and the locus coeruleus-norepinephrine system. The reasons why the prevalence of depression is twice as high in females as in males are as follows: first, estrogen increases the expression of CRF in hypothalamus; second, the locus coeruleus-norepinephrine system is activated and maintains hyperarousal due to sex/gender differences in the signaling system downstream of CRF_1 [5] (Fig. 21.6a); and third, the limbic input according to emotional changes is more effectively received in females, as dendrites in the locus coeruleus nerves are more abundant in females than in males [5] (Fig. 21.6b). There are sex/gender differences in the locus coeruleus dendrites. While the number of dendrites is small in males, dendrites are abundant in females, allowing them to receive information very well from the limbic system. CRF_1 receptors distributed in the locus coeruleus dendrites are connected to β-arrestin-2 and exist in the cytoplasm in males, while they are mainly distributed in the cell membranes after combining with Gs located in the cell membranes, rather than β-arrestin-2, in females [5] (Fig. 21.6b). As a result, inter-communication with the locus coeruleus nerve dendrites is very active, making it easy to maintain hyperarousal. Fourth, when an excessive amount of CRF is secreted after a stressor, the CRF_1 receptors are inside the cytoplasm for negative feedback in males, but in females, the connection between CRF_1 and β-arrestin-2 does not exist, and instead CRF_1 binds with Gs in the cell membranes, where Gs remain present. As a result, negative feedback in response to CRF over-secretion does not occur in females, so the HPA axis and the locus coeruleus-norepinephrine system continue to be activated and hyperarousal maintained, leading to disease manifestations such as stomach pain due to visceral hypersensitivity.

21.4.4.4 The Role of the CRF Signaling Pathway in the Gastrointestinal Tract

CRF ligand and receptors exist in various organs other than in the CNS and are widely distributed in the GI tract [84]. CRF_1 in the GI

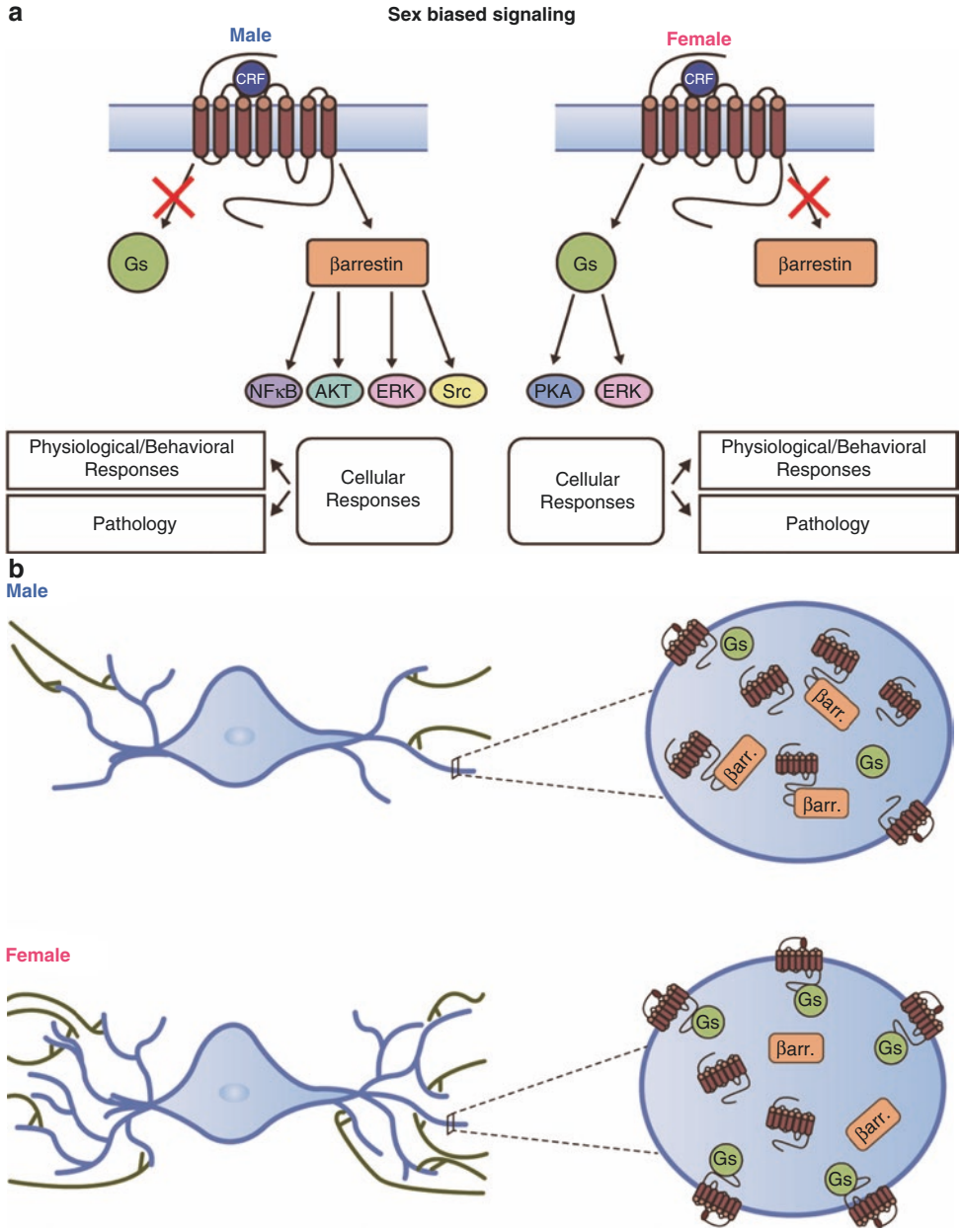

Fig. 21.6 Schematic of corticotropin-releasing factor receptor 1 (CRF_1 receptor) and locus coeruleus nerve cells by sex/gender. (**a**) Sex/gender differences are observed as β-arrestin-2 controls the effect of CRF_1 receptors using G-protein-independent signaling cascades such as mitogen-activated protein kinase (e.g., ERK2, JNK3, and p38), tyrosine kinases (e.g., c-SRC, Hck, Fgr, Yes), AKT, PI3 kinase, and RhoA through scaffolding signaling molecules in males, while CRF_1 receptors in females do not interact with β-arrestin-2 and instead compose a signaling system different from that of males depending on GTP-binding proteins (Gs). (**b**) These are sex/gender differences in the locus coeruleus dendrites. While the number of dendrites is small in males, these dendrites are abundant in females, allowing them to receive information very well from the limbic system. CRF_1 receptors distributed in the locus coeruleus dendrites are connected to β-arrestin-2 (square box) and exist in the cytoplasm in males, while they are mainly distributed in the cell membranes after binding with Gs located in the cell membranes, rather than β-arrestin-2, in females. As a result, it is easy to maintain hyperarousal after stress in females due to active inter-communication with locus coeruleus dendrites (adapted from Bangasser and Valentino [5])

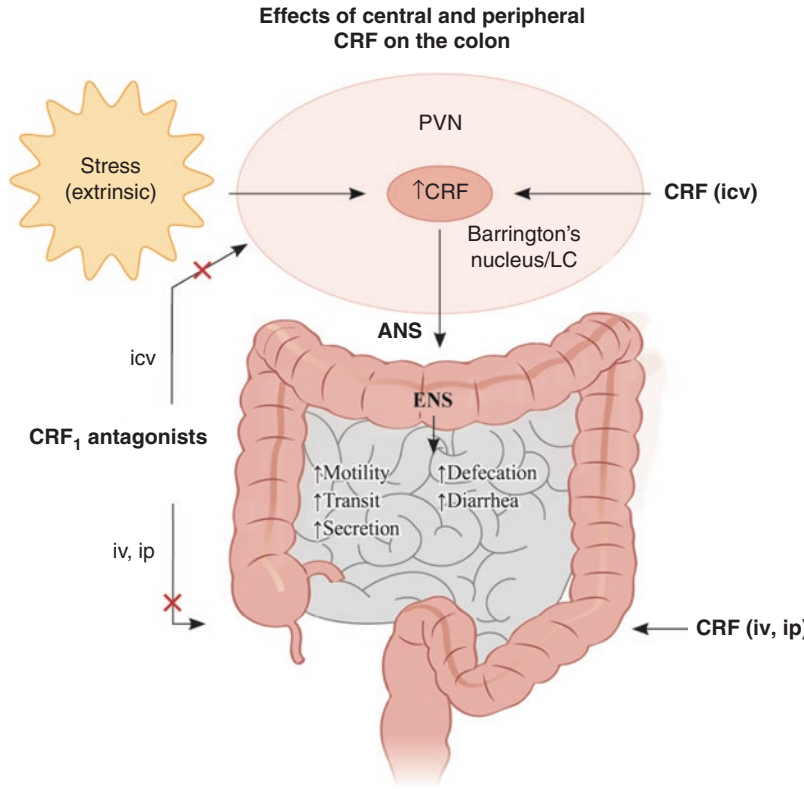

Fig. 21.7 The role of corticotropin-releasing factor (CRF) on intestinal function. CRF, which is increased due to stress, causes significant changes in intestinal motility and intestinal transit time through the autonomic nervous system and visceral nervous system and increases peristalsis (adapted from Stengel and Taché [114])

tract, in particular, is related to the increase in intestinal motility [113], and the local effect of CRF in these peripheral areas is partly responsible for changes in intestinal motility due to stress [114]. When CRF is intravenously injected, significant changes in intestinal motility and the intestinal transit time can be observed [88, 115]. When CRF is injected into isolated intestinal tissue, an increase in peristalsis occurs [93]. Figure 21.7 presents this process schematically [114].

21.4.4.5 The Effect of Stress on Gastrointestinal Inflammation

Factors that cause inflammation in the intestinal tract for patients with IBS are bacterial or viral infections, genetic factors, food allergies, stress, changes in the gut microbiome, and malabsorption of bile acids. It is unclear whether stress acts as a direct cause of intestinal inflammation, but it can be a factor that increases activation of mucosal inflammatory cells, especially mast cells.

When acute stress is introduced in animal studies, intestinal permeability and ion secretion increase [116, 117]. When chronic psychological stress is introduced, increases in the number and degranulation of intestinal mast cells occur with the increase in intestinal permeability [118]. Intestinal mast cells are activated by CRF or acetylcholine secreted in the nerve endings originating from central nerves [118, 119]. Therefore, when the blood CRF level increases due to stress, secretion of mediating substances increases due to activation of mast cells, and the permeability of intestinal mucosa increases, causing inflammation [120] (Fig. 21.8).

21.4.4.6 Stress and Postinfectious Irritable Bowel Syndrome

IBS is related to the interaction of the gut-microbiome-brain axis, and it has been reported that psychological stress around the time that an intestinal infection occurred was significantly higher in patients with IBS group than in controls [121]. Since there has been a report

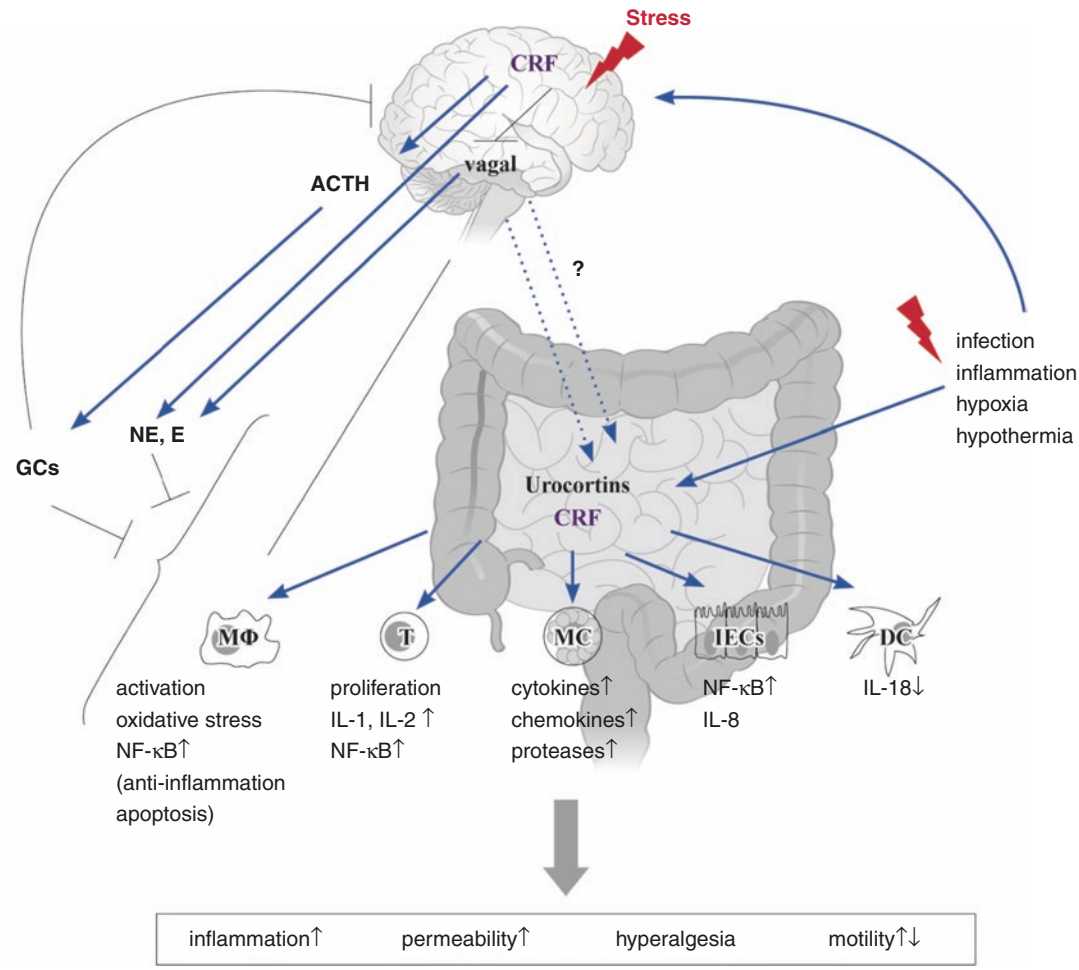

Fig. 21.8 The role of corticotropin-releasing factor (CRF) in the gastrointestinal immune system and inflammation. When the blood CRF level increases due to stress, activation of the hypothalamus-pituitary-adrenal axis (HPA axis) such as adrenocorticotropic hormone (ACTH), glucocorticoid, and corticosterone; activation of the arousal system of norepinephrine; and activation of various immune cells such as mast cells increase the secretion of cytokines and the permeability of intestinal mucosa, causing inflammation. *CRF* corticotropin-releasing factor, *DC* dendritic cells, *E* epinephrine, *GC* circulating glucorcorticoids, *IEC* intestinal epithelial cells, *MC* mucosal mast cells, *MΦ* macrophages, *NE* norepinephrine, *T* T lymphocytes (adapted from Kiank et al. [120])

that visceral sensation and motility did not significantly differ between patients with postinfectious IBS and controls, it is hypothesized that symptoms are maintained because stress is recognized in the form of increased signaling when the CNS processes information delivered from the intestines [122]. HPA axis activation due to stress can also cause an increase in inflammatory cells and mediators in the GI tract [123]. Therefore, functional disorders in the brain-gut interaction act as an important component of the pathophysiology of postinfectious IBS. The role of CRF in the GI immune system and inflammation can be summarized as follows: when the blood CRF level increases due to stress, activation of the HPA axis (including ACTH, glucocorticoid, and corticosterone), the arousal system involving norepinephrine, and various immune cells such as mast cells increases the secretion of cytokines and the permeability of the intestinal mucosa, causing inflammation [120] (Fig. 21.8).

21.5 Conclusions

Disorders in GI motility, visceral hypersensitivity, infection, inflammation, and changes in the gut microbiota are hypothesized to be important mechanisms of the pathophysiology of FGIDs. The concept of the CNS- GI -gut microbiota axis, by which GI symptoms occur as a result of sensation disorders, changes in motility, combined activation of the ANS and CNS, and the effect of gut microbiota, has been suggested. The gut-microbiome-brain axis refers to the interactions that occur among the CNS, gut microbiome, and areas that express actual function such as GI sensation and motility, and this axis has been hypothesized as an important component of the pathophysiology of FGIDs. The mechanism that controls GI sensation and motility in the CNS and the area responsible for emotions and cognitions can be observed using fMRI. It has been reported that there are both functional and structural changes in the brain of patients with IBS and that there are sex/gender differences in these changes. The reason why women are more vulnerable to stress responses is due to a higher sensitivity of their locus coeruleus-norepinephrine system to CRF and stress. Stress increases blood CRF levels to a greater extent in females, activating the HPA axis (including ACTH, glucocorticoid, and corticosterone), the norepinephrine system, and various immune cells including mast cells. This activation then increases the secretion of cytokines and the permeability of intestinal mucosa, thereby causing inflammation in the GI system. Therefore, for the tailored treatment for FGIDs, the recognition of basic sex/gender differences in the gut-microbiome-brain axis is necessary.

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Part X

Sex Difference of Gut or Oral Microbiota

Sex Difference of Gut Microbiota

22

Nayoung Kim

22.1 Introduction

The microbiome refers to the combined total of microbes that exist in a certain environment. Although 99% of the microbes in the human body are bacteria, other forms such as viruses, archaea, fungi, and protozoa exist as well. The digestive system, including the intestines, contains 95% of the total microbes in the human body, while the remaining 1% are widely distributed in the respiratory organs, reproductive organs, mouth, and skin. Therefore, many scholars have focused on studying the gut microbiome. It was thought that the number of symbiotic microbes is more than 10 times higher than the number of somatic cells that compose the human body, but recent study results have calculated the number of symbiotic microbes at 4×10^{13}, which is slightly more than the number of somatic cells. Symbiotic microbes make up 200 g to 1 kg of the total body weight. The gut microbiota that comprise the majority of the symbiotic microbes contribute to the development of immune organs and the visceral plexus after birth, engage in important immune responses, modulate the response to medications, and have a large effect on metabolism. As next-generation sequencing (NGS) was widely implemented starting in the 2000s, research on metagenomics became very active. Research within this framework has demonstrated that the composition of the gut microbiota is influenced by diet, ethnicity, age, antibiotics, stress, psychological factors, the health of pregnant mothers, the method of delivery (i.e., vaginal delivery vs. cesarean section), environmental factors, and exercise [1]. Sex hormones vary across childhood, puberty (when sex/gender differences start to be observed), pregnancy trimester, menopause, and old age; but the importance of sex/gender differences is often overlooked in gut microbiome research [2]. Simultaneously, estrogen and androgens, the most widely known sex hormones, influence the gut microbiome, which in turn influences the metabolism of estrogen and androgen. As this relationship became understood, the term "microgenderome" was created [3], but this concept is not yet widely known. This chapter explores the sex/gender differences in the dynamic gut microbiome, and its associations with age.

22.2 Factors that Influence the Distribution of Gut Microbiome

The gut microbiome changes drastically by age as the gut microbiota are influenced by both differences in sex hormones and diet and other various environmental factors according to age. The

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role of the gut microbiota is to stimulate maturation of the immune system, which protects against the invasion of pathogens through interactions with the body, and to engage in the regulation of metabolism by producing vitamins and short-chain fatty acids (SCFAs) as a supply of nutrition. However, if the interactions that maintain homeostasis are interrupted or dysbiosis of the gut microbiota occurs, health can deteriorate and disease occurs. The human gut microbiome can be categorized into the mucosal gut microbiota, which are attached to the intestinal epithelial cells, and the luminal microbiota, which exist in the intestinal lumen [4] (Fig. 22.1). They activate homeostatic reactions by epithelial cells, macrophages, dendritic cells, T lymphocytes, and B lymphocytes to allow coexistence with potential pathogenic bacterial products in the intestines. Pattern recognition receptors including extracellular toll-like receptor (TLR) and intracellular NOD-like receptor (NLR) recognize bacteria, and their binding with bacterial receptors activates central signaling pathways, such as the nuclear transcription factor–kappa B (NF-κB), AKT/PI3K, and MAPK pathways. The gut microbiota induce inhibitory substances such as A20, PPARγ, NF-κB inhibitors, interferon (IFN) α/β, interleukin (IL)-10, transforming growth factor (TGF)-β, and prostaglandin E_2 (PGE_2). The role of the gut microbiota in the normal state is to control pathogenic innate immunity and to promote the immune system through adaptive immunity in the intestinal mucosa. There is a slight difference in the distribution of the phyla of the gut microbiota between patients with irritable bowel syndrome and controls, with the highest proportion found for Firmicutes, followed in descending order by Bacteroidetes, Actinobacteria, and Verrucomicrobia [5] (Fig. 22.2). This distribution changes according to various factors including diet, ethnicity, age, and sex/gender. The ratio of bacteria to human

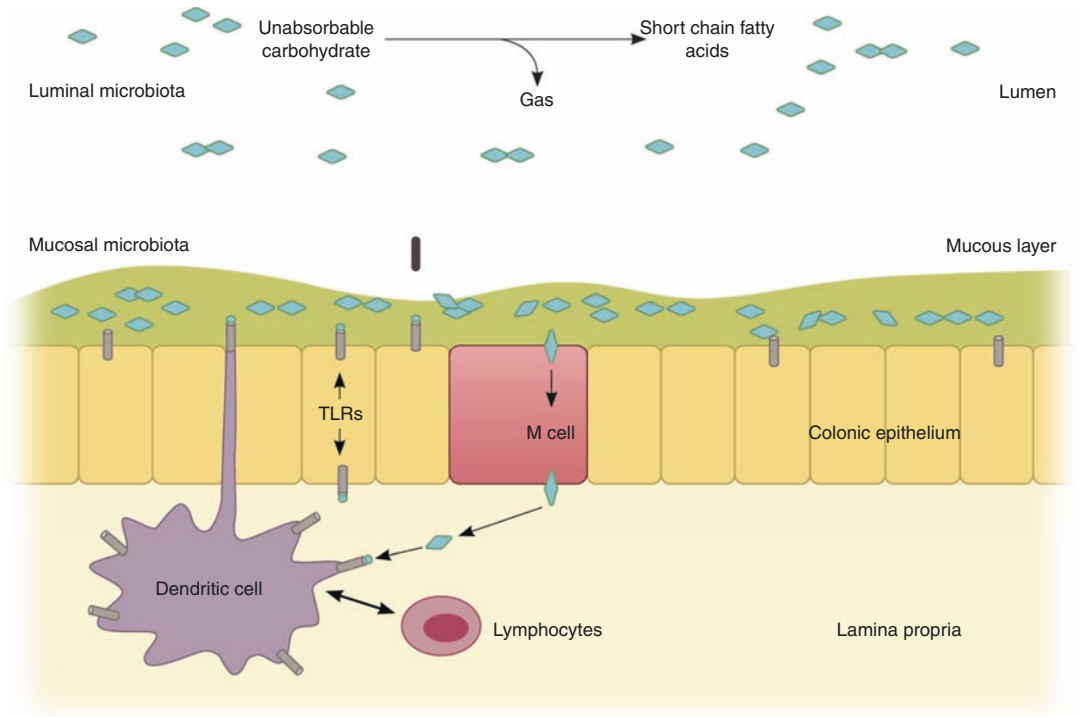


Fig. 22.1 Categorization of the gut microbiota. The gut microbiome can be categorized into the mucosal gut microbiota, which exist attached to the intestinal epithelial cells, and the luminal microbiota, which exist in the intestinal lumen separated from epithelial cells. *TLR* toll-like receptor (adapted from Seo et al. [4])

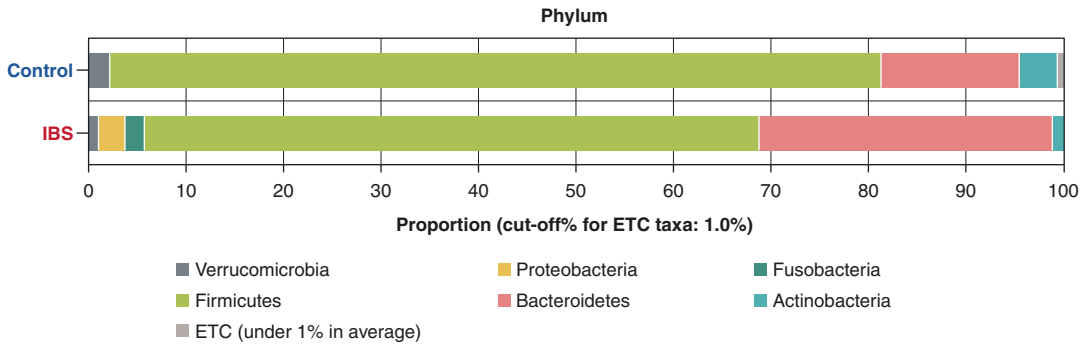


Fig. 22.2 Comparison of gut microbiota in the stool of healthy individuals and patients with irritable bowel syndrome. When the stool of patients with irritable bowel syndrome was analyzed, the level of Firmicutes was lower, that of Bacteroidetes was twice as high, and those of the Proteobacteria and Fusobacteria phyla was higher than in controls. (modified from Lee et al. [5])

cells (B:H ratio) was 2.2 in females, which is markedly higher than the ratio of 1.3 in males [6–11] (Table 22.1), making it important to distinguish sex/gender in interpreting research results. Other than intestinal bacteria, another subset of the gut microbiota that is receiving attention is fungi, which comprise less than 0.1% of the gut microbiota. Most of the fungi found in the intestines are *Candida albicans*, but *Torulopsis glabrata* and *Candida tropicalis* have also been reported [12]. *Saccharomyces boulardii* is used in *Lactobacillus* formulations to treat diarrhea [12]. Reports have found that the diversity of intestinal mucosal fungi increased in patients with colon cancer [13] and that the percentage of *Basidiomycota* increased in the mucosa of patients with colitis-related colon cancer, indicating that fungi might be involved in the dysbiosis of gut microbiota in patients with colon cancer [13]. Research on intestinal fungi is in its early stages, and no studies have investigated sex differences.

22.2.1 Differences in Gut Microbiota by Diet and Ethnicity

The gut microbiota, especially *Faecalibacterium*, *Roseburia*, and *Bifidobacterium*, metabolize consumed dietary fibers into SCFAs, which is beneficial because SCFAs correspond to 10% of the energy source of the human body. The gut microbiota also metabolize bile acid, which in turn affects the diversity and gene expression of gut microbiota [14]. SCFAs include acetate, propionate, and butyrate, which are energy sources, modulate inflammation, and play an important role in intestinal motility and wound healing [15]. Diet also influences the health of the human body by controlling the composition of the gut microbiota. According to a study that analyzed the stool of 98 individuals, *Bacteroides* and *Prevotella* were dominant clusters among the fecal microbes. When proteins or food rich in animal fat were consumed as part of a long-term diet, *Bacteroides* increased, whereas *Prevotella* increased when food rich in carbohydrates was consumed [16]. These changes in the gut microbiota according to diet are observed starting in childhood. In a study that compared children living in Italian cities and in rural areas in Africa, 14 healthy African children generated energy from fiber, as they had abundant *Prevotella* and *Xylanibacter*, which hydrolyze fiber and sugar, and showed rich biodiversity [16]. Compared to children in Italian cities, their levels of SCFAs and butyrate, which are effective for preventing colon cancer, were higher, and the numbers of *E. coli*, *Shigella*, and *Salmonella* were lower in African children [16]. Unfortunately, this study did not report the sex/gender of the children. However, as the children were pre-pubescent and the sample size was small, it would have been difficult to see sex/gender differences.

Table 22.1 The proportion of intestinal bacteria to human cells by sex/gender (adapted from Sender et al. [6])

Population segment	Body weight (kg)	Age (y)	Blood volume (L)	RBC count (10^{12}/L)	Colon content (g)	bac. conc. (10^{11}/g wet)[a]	Total human cells (10^{12})[b]	Total bacteria (10^{12})	B:H
Ref. man	70	20–30	4.9	5.0	420	0.92	30	38	1.3
Ref. woman	63		3.9	4.5	480	0.92	21	44	2.2
Young infant	4.4	4 weeks	0.4	3.8	48	0.92	1.9	4.4	2.3
Infant	9.6	1	0.8	4.5	80	0.92	4	7	1.7
Elder	70	66	3.8[c]	4.8	420	0.92	22	38	1.8
Obese	140		6.7	5.0[d]	610[e]	0.92	40	56	1.4

The ratio is 2.2 in females, which is greater than that of 1.3 in males

[a] No significant change in bacteria concentrations in relation to high variation for the reference man [7, 8]

[b] Assuming RBCs account for 84% of the total host cells as observed for the reference man

[c] Decrease of 24% in the blood volume, according to [9]

[d] No significant change in the hematocrit in obesity [10]

[e] We could not find any direct measurements of the colonic volume for obese individuals in the literature, yet from an indirect analysis, the volume increases with weight and plateaus at about 600 mL [11]

Research on changes of gut microbiota in response to a high-fat diet is an important issue in the studies regarding the effect of diet on gut microbiota. In a study with F344 mice conducted by the author's research team, a high-fat diet in which 60% of the total calories came from fat was given for 8 weeks [17]. Whereas 6-week-old (equivalent to 6 years old in humans) male and female mice and 2-year-old (equivalent to 80 years old in humans) female mice effectively reorganized the gut microbiota to resolve high fat, this reorganization was not observed in 2-year-old male mice [17]. Previously it was known that a long period of time (around 6 months) was necessary until diet's effect became definite on the gut microbiota. However, recent studies in mice indicated that diet had an immediate effect on gut microbiota, as a high-fat diet resulted in a difference even in a day [18]. The result might be influenced by the short doubling time of *E. coli* (20 min) and fast metabolism in mice. However, it can be inferred that the diet's effects on gut microbiota occur in a shorter time period in the human body as well. Considering national and international reports [19, 20] that women tend to prefer fruits and vegetables more than men, sex/gender differences in the gut microbiota can be partially attributed to sex/gender differences in diet, and the effect of diet can vary by age.

22.2.2 Changes in Gut Microbiota by Age

It has been reported that there are generally no sex/gender differences in the gut microbiota in childhood, which might be due to the absence of differences in sex hormones before puberty [21]. Sex/gender differences in the gut microbiota are first observed in puberty and continue until old age because the maturation of the intestines is proportional to hormonal changes, which are reflected in the changes in gut microbiota [21].

22.2.2.1 Gut Microbiota of Fetuses and Mothers

The gut microbiota during pregnancy tend to be different from those of females pre-pregnancy. In addition, there are large changes depending on trimester [22] (Fig. 22.3). During pregnancy, the richness of diversity decreases as Proteobacteria and Actinobacteria increase. When the stool of pregnant female in their third trimester (T3) was transplanted into germ-free mice, fat and insulin resistance developed in mice, but the difference was small when using stool from female in their first trimester (T1) [22]. Of particular interest, the composition of the gut microbiota (Fig. 22.3b) was different in the T1 and the T3, when the levels of estrogen differ (Fig. 22.3a), and there were large differences in the α-diversity in T3 [22] (Fig. 22.3c). The α-diversity in T3, when the level of estrogen is highest, was lower than that in T1 (Fig. 22.3c), and this difference furnishes evidence that female sex hormones influence the gut microbiota.

It is becoming understood that the metabolic requirements in stages of fetal development are different by sex [23, 24]. The maternal gut microbiota appropriately respond to fetal requirements and provide nutrients and metabolic products needed by the fetus [22]. In T1, the gut microbiota in the Clostridiales order, which produce SCFAs such as butyrate, propionate, and acetate, increase substantially [22, 25]. The increased blood SCFAs in mothers cross the placenta and influence the development of the fetal brain [26]. Increased butyrate levels during early pregnancy follow the same trajectory as the development of blood-brain barrier (BBB), and it was proven that the gut microbiota that produce butyrate increased in early-pregnancy mice [27]. Dynamic remodeling is observed in the late stages of human pregnancy as the gut microbiota that produce SCFAs decrease, while the gut microbiota that produce energy increases [22], but sex differences among fetuses in this process are not understood in detail.

22.2.2.2 Gut Microbiota After Birth

The moment a fetus is born, there is a large change in the gut microbiota. For several days or weeks after birth, *Bacteroides*, *Bifidobacterium*, *Parabacteroides*, and *Escherichia/Shigella* compose the majority of the gut microbiota of newborns [28]. *Escherichia/Shigella* belongs to the

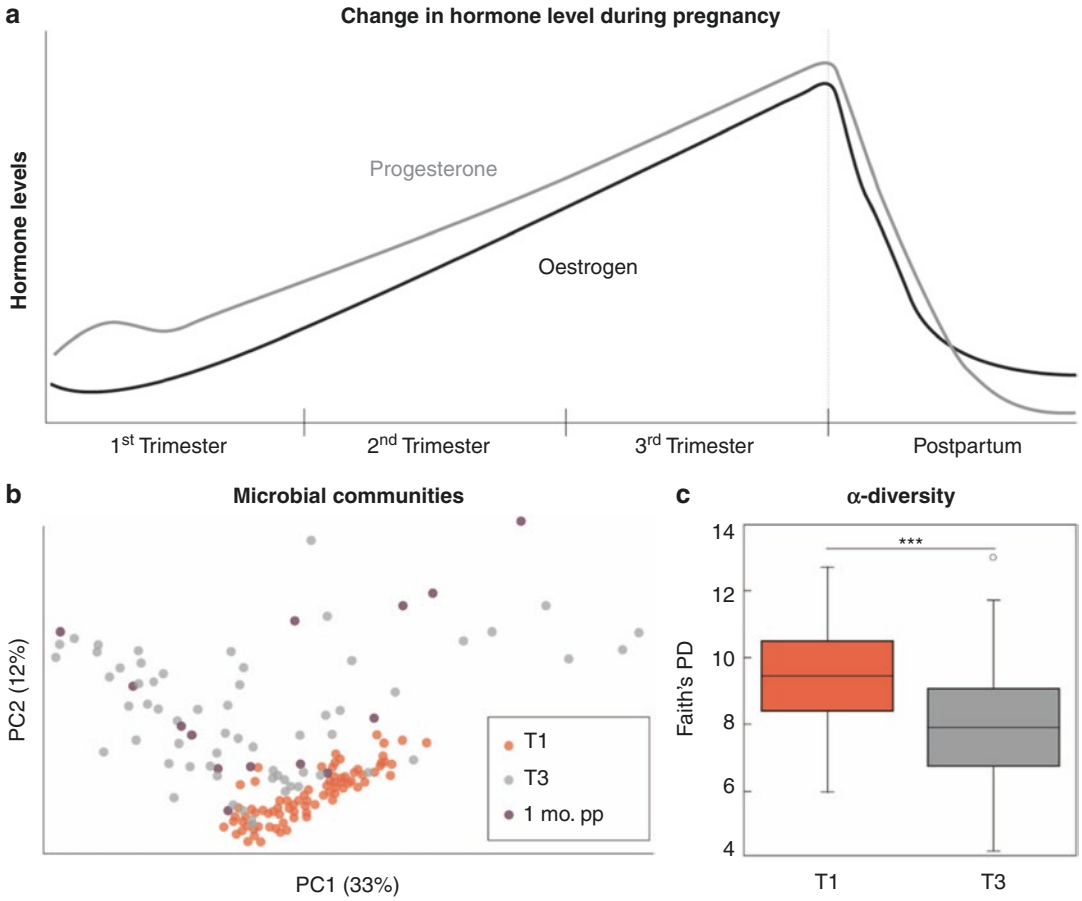


Fig. 22.3 Composition trends of the gut microbiota and changes in hormones by stages of pregnancy. There are clear differences in gut microbiota during pregnancy. Compared to the first trimester (T1), when the levels of estrogen and progesterone are the highest (**a**), the gut microbiota in the third trimester (T3) are different (**b**), and α-diversity (**c**) is lower. *mo* month (adapted from Koren et al. [22])

Gram-negative Proteobacteria phylum, and lipopolysaccharide (LPS), which causes immune responses, is distributed in the outer membrane of *Escherichia/Shigella* [29, 30]. It is known that LPS derived from Proteobacteria directly enters through the vagus nerve or stimulates cytokines produced through paracrine or endocrine mechanisms to cross the BBB to aid neurodevelopment [31]. A recent study found that the gut microbiota stimulates immune cells such as microglia in the brain to cause sex differences in the function of microglia [32].

There are differences in the gut microbiota of newborns depending on the delivery method. Bacteria from the mother's vagina comprise most of the gut microbiota of newborns delivered through vaginal birth, but the gut microbiome of newborns delivered through cesarean section is composed of bacteria from the mother's skin, the environment to which the infant is exposed, the medical staff participating in the delivery, and other newborns [33]. The difference in the gut microbiota by delivery method is maintained until childhood and is associated with increased body mass index or childhood obesity [34]. Newborns delivered through cesarean section tend to have allergies such as rhinoconjunctivitis, which is most common among female newborns delivered by cesarean section in women who have previously undergone at least one cesarean

section [35, 36]. According to meta-analyses, children born through cesarean section have a higher risk of autistic disorders, and one of the suggested causes is the difference in the gut microbiota by the delivery method [37, 38]. Male children are more strongly impacted by maternal stress, which is interpreted as reflecting sex differences in the gut microbiota. Research on this topic is conducted through measurements of spatial learning, locomotor activity according to stress, and sucrose preference [39–46]; and the mechanism by which male children are influenced more is explained as follows. Stress in pregnant mothers reduces *Lactobacillus*, which is the most common taxon in the vagina and vaginal immune activity, as well as the most common resident flora in newborns' intestines [47]. The decrease in *Lactobacillus* interferes with the composition of breast milk because they produce lactic acid; therefore, an insufficient amount of *Lactobacillus* lengthens the time needed to establish an acidic gut environment, which is an important transition in infancy [48–50]. An increase in anaerobic bacteria such as *Bacteroides* and *Clostridium* due to a decrease in *Lactobacillus* was only observed in male children. Changes in the composition of gut microbiota in newborns cause disruptions in the supply of histidine and glutamate, which are important nutrients for brain development, but were not observed in female children [51, 52]. Summarizing the evidence so far, the vaginal microbiota of mothers influence the gut microbiota of newborns differently by sex, and stress before birth is an important aspect of sex differences in the development of the intestines and the brain.

22.2.2.3 Gut Microbiota During Childhood and Puberty

Changes in the composition and function of gut microbiota occur during childhood and puberty. The composition of the microbiota becomes more complex, and the gut microbiota tend to be more unstable than in adults [53]. It is known that there are no sex differences in childhood due to the lack of sex hormone signaling. Sex differences in the gut microbiota start to occur during puberty [54]. According to studies in mice, the changes during puberty are further altered through maturation during adulthood in male mice, but in female mice, changes during puberty are maintained through adulthood [55]. As evidence, when male mice are neutered during puberty to reduce testosterone, sex differences in gut microbiota do not occur in adulthood, indicating that testosterone affects the composition of dimorphic gut microbiota [55]. Interestingly, when the cecal content, which is more diverse and abundant in adult male mice, was injected into pubescent female mice, the gut microbiota and metabolites in the female mice showed a more masculine pattern, and testosterone increased and was maintained until adulthood in female mice [56]. Moreover, when the cecal content of adult male mice and flutamide, an androgen receptor antagonist, were injected into female mice together, the gut microbiota did not show a masculine pattern, indicating that the increase in testosterone is imperative for downstream changes in the gut microbiota from the transplantation of male cecal content [56]. In contrast, when the intestinal content of female mice was given to male mice, estrogen levels did not increase and female characteristics did not develop, showing sex differences [21].

22.2.2.4 Changes in the Gut Microbiota in Adulthood and Old Age

The changes in the gut microbiota that occur during the transitional phase from puberty to adulthood are directed toward better adaptation to stress, infection, diet, and antibiotics [57]. Chronic social stress destroys intestinal barrier function and changes the bacterial composition. The intestinal epithelial immune response is activated as bacteria can more easily approach the lymphatic tissue. In this process, males have more *Bacteroides* and *Prevotella* than females, demonstrating a sex difference in stress and gut microbiota [58]. Males and females in adulthood display sex differences in hormonal changes. Males maintain a steady level of testosterone, whereas females regularly have hormonal changes, ultimately resulting in differences in the gut microbiota [59, 60]. The famous ELDERMET

consortium listed the health-related aging signs associated with the gut microbiota as frailty, nutritional status, metabolism score, and changes in inflammation markers [61–63]. The core changes in the gut microbiota with age are an increased proportion of *Bacteroides* species and *Clostridium* bacteria [61]. An increase in Firmicutes and anaerobic bacteria is characteristic in people over the age of 100 [64], and among individuals older than 70, the physiological function of the intestines affects the composition of gut microbiota [54, 65, 66]. For example, the quantity of the gut microbiota of patients with constipation increases proportionally to the intestinal transit time [67]. As the stool became harder and the number of *Methanobrevibacter* and *Akkermansia* bacteria increased, the Ruminococcaceae-*Bacteroides* enterotype increased [67]. In contrast, in patients with diarrhea or loose stool with a fast intestinal transit time, Firmicutes (*Faecalibacterium*, *Lactococcus*, *Roseburia*) and *Prevotella* enterotypes increased [68]. According to a study with 35,292 German adults, there were age differences in the number of colony-forming units. For example, *E. coli* and *Enterococci* spp. increased with age, and *Bacteroides* spp. decreased with age, while there were no changes in *Lactobacilli* and *Bifidobacteria* [65, 69]. In a study by the author's research team that directly measured SCFAs in the cecal content of male mice aged 6 weeks, 31 weeks, 74 weeks, and 2 years, Lachnospiraceae, which mainly produce SCFAs, and EU622775_s and EU622773_s, which have a strong association with butyrate, increased in 31-week-old male mice (human age of 30 years), showing age differences [70]. It is regrettable that sex differences in the gut microbiota that produce SCFAs were not examined, as comparisons with female mice were not made.

22.2.2.5 Changes in the Gut Microbiota Before and After Menopause

Aging is a very dynamic process for females, in whom ovarian activity decreases and hormones change rapidly. The composition of gut microbiota is different between before and after menopause (Fig. 22.4a), and the ratio of Firmicutes to Bacteroidetes increases after menopause to a level greater than that of males ($p = 0.013$) [71] (Fig. 22.4b). Moreover, the ratio of *Lachnospira* and *Roseburia, Prevotella*, *Parabacteroides*, and *Bilophila genera*, as well as plasma glucagon-like peptide-1 (GLP-1), IL-6, and MCP-1 levels increased after menopause [71], indicating that hormonal changes have a major effect on the gut microbiota.

22.3 Sex Differences in the Gut Microbiota

As humans age, the gut microbiota matures, and changes in sex hormones occur. The gut microbiota and sex hormones have a close relationship [21]. In a study with 1135 individuals, females had substantial diversity in the gut microbiota, which was influenced by birth control pills or ovariectomy, and had antibiotic resistance genes, which might have been related to the frequent use of antibiotics [72]. Numerous studies about the sex differences of gut microbiota are being published [6, 73] (Table 22.1) as more detailed information is available since the NGS method became more elaborated in 2014.

22.3.1 Relationship Between Sex Hormones and the Gut Microbiota

Sex hormones affect gut microbiota, especially through the immune activity. In addition, both of estrogen and androgens are affected by gut microbiota, especially, by β-glucuronidase producing microbiota in the menopause and in old male. It means there is a similarity in the metabolism of sex hormones in male and female in terms of gut microbiota.

22.3.1.1 Estrogen and Gut Microbiota

Reproductive organs are controlled by various hormones through intricate feedback, and the organs that secrete estrogen are the ovaries, adrenal cortex, and adipose tissue. Estrogen directly

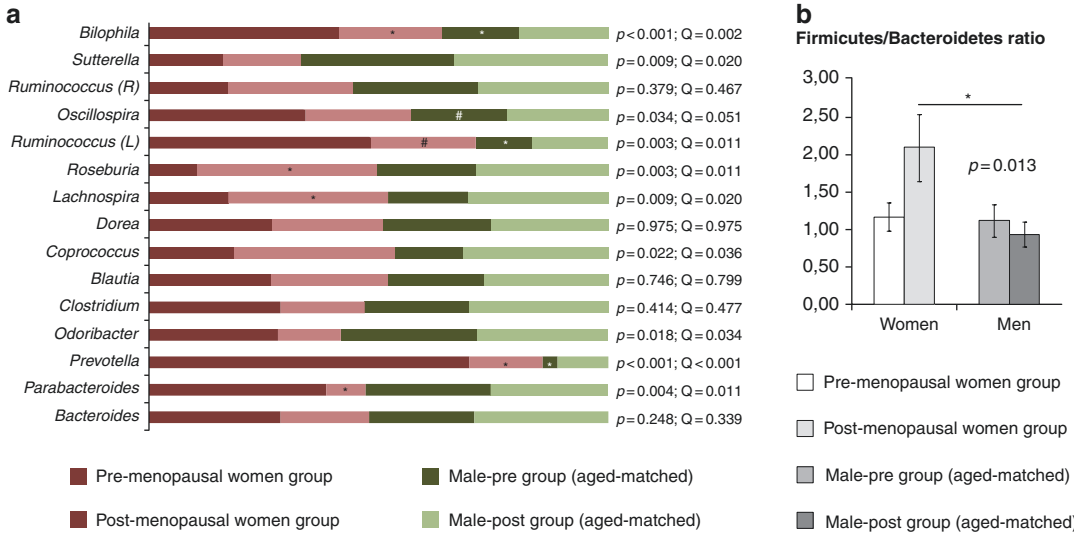


Fig. 22.4 Changes in the gut microbiota post-menopause. The composition of the gut microbiota pre- and post-menopause differs (**a**), and the ratio of Firmicutes to Bacteroidetes increases to a level higher than that of males after menopause (**b**) (adapted from Santos-Marcos et al. [71])

controls the metabolism of bacteria through the combination with estrogen receptor beta (ERβ) [74], and bacteria are also actively involved in the metabolism of estrogen [3].

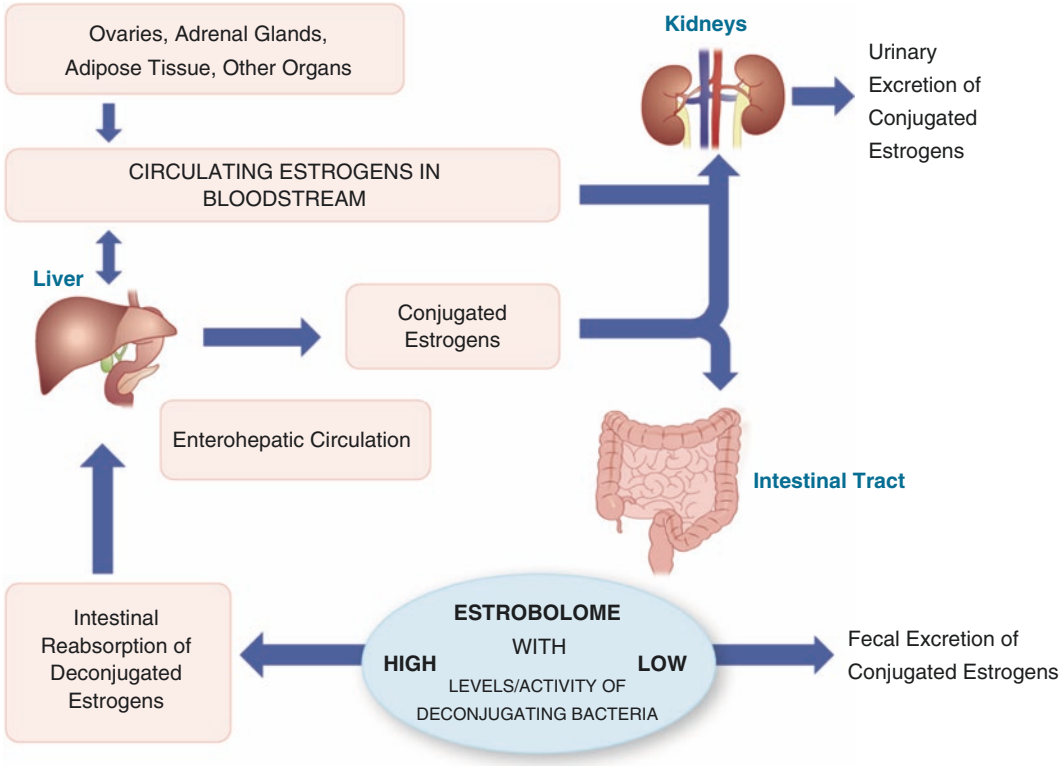
22.3.1.1.1 Modulation of the Gut Microbiota by Estrogen

Estrogen and testosterone have a direct impact on the gut microbiota and immune cells. β-estradiol stimulates dendritic cells to secrete IL-12 and IFN-γ, which in turn activate the secretion of pro-inflammatory cytokines [75]. β-estradiol extends the survival of B lymphocytes and activates polyclonal B lymphocytes, increasing intestinal permeability and creating a proinflammatory environment, which creates an inflammation process loop as the gut microbiota migrate to the lamina propria, causing inflammation [75]. There are conflicting reports stating that 17β-estradiol reduced metabolic endotoxemia and low-grade chronic inflammation [76]. Male mice treated with 17β-estradiol showed a decreased production of Proteobacteria and LPS, and metabolic endotoxemia and low-grade chronic inflammation increased in female mice that underwent ovariectomy [76]. The results indicated that estrogen itself influences the composition of gut microbiota, increases intestinal permeability through its ongoing effects on immune cells, and affects the composition of the gut microbiota.

22.3.1.1.2 Involvement of the Gut Microbiota in the Metabolism of Estrogen

The gut microbiota are not only influenced by estrogen, but also engage in the metabolism of estrogen [3]. When conjugated estrogens are secreted into the bile and kidney after circulating in blood, β-glucuronidase in gut microbiota mutates the estrogen that flows into the bile into its deconjugated forms [3] (Fig. 22.5a). This active deconjugated estrogen is absorbed into the blood and enters the enterohepatic circulation to act on ERα and ERβ in the reproductive organs, muscle, nervous system, and vasculature [3] (Fig. 22.5a). Some taxa in the gut microbiota are rich in β-glucuronidase, while others do not have it, limiting the bacteria that can influence the blood levels of estrogen [3] (Fig. 22.5b). ERs are widely distributed in the central nervous system and visceral nervous system. After estrogen binds with ERs, the hormone-receptor complex combines with the ligand-binding site of ERs that exist in the nucleus to cause morphological changes [77]. This becomes the ligand-ER com-

a



b

Genus	β-glucuronidase	β-galactosidase
Collinsella	+	-
Edwardsiella	+	-
Alistipes	+	+
Bacteroides	+	+
Bifidobacterium	+	+
Citrobacter	+	+
Clostridium	+	+
Dermabacter	+	+
Escherichia	+	+

Genus	β-glucuronidase	β-galactosidase
Faecalibacterium	+	+
Lactobacillus	+	+
Marvinbryantia	+	+
Propionibacterium	+	+
Roseburia	+	+
Tannerella	+	+
Actinomyces	-	+
Alistipes	-	+

Fig. 22.5 Metabolic processes of estrogen by gut microbiota. When conjugated estrogen is secreted into the kidney and stool, β-glucuronidase converts conjugated estrogens into their deconjugated forms. Active deconjugated estrogen is absorbed into the blood and enters enterohepatic circulation to act on the estrogen receptors ERα and ERβ (**a**). Bacteria that secrete β-glucuronidase (**b**) (adapted from Kwa et al. [3])

plex, which interacts with estrogen-responsive elements (EREs) located in gene promoters. This complex operates with various co-activators and co-repressor multiprotein complexes that promote or repress gene transcription [77].

An association was found between total estrogen levels in the urine and the richness and α-diversity of fecal bacteria among males and menopausal females. Estrogen secreted in organs other than the ovaries was associated with fecal

Clostridia and Ruminococcaceae, and the activity of fecal β-glucuronidase was inversely associated with fecal estrogen [73]. However, the results were different in pre-menopausal females, indicating that ovarian estrogen and non-ovarian estrogen are affected differently by the involvement of the gut microbiota in estrogen metabolism [78]. In pre-menopausal women, estrogen was not related to gut microbiota or its enzymes, and non-ovarian estrogen was associated with gut microbiota and β-glucuronidase [78].

22.3.1.2 Androgens and the Gut Microbiota

Metabolism of androgens is also affected by β-glucuronidase gut microbiota which is very similar to that of estrogen. In addition, patients with polycystic ovary syndrome (PCOS) show the symptoms related with androgens excess.

22.3.1.2.1 The Effect of Gut Microbiota on the Metabolism of Androgens

There are deconjugated and glucuronidated forms of androgens. In mice, the levels of glucuronidated testosterone and dihydrotestosterone (DHT) were high in the small intestines, while the level of free DHT type was high at the end of the large intestines [79]. In young male mice, the level of free DHT was 70 times higher in the stool than in the blood serum, and in germ-free mice, glucuronidated testosterone and DHT levels were high, but the free DHT level was low, indicating that the gut microbiota engage in the deglucuronidation of androgen [79]. Moreover, when the associations between testosterone in males and estrogen in females and the gut microbiota were examined, the diversity of gut microbiota was greater in males with high testosterone and females with high estrogen levels [80]. *Acinetobacter*, *Dorea*, *Ruminococcus*, and *Megamonas* were prevalent in males with high testosterone levels, and Bacteroidetes were prevalent, while Firmicutes were less prevalent in females with high estrogen levels. Females with low estrogen levels had more *Slackia* and *Butyricimonas* genera [80].

The effect of sex hormones on immune cells is also different. In males, testosterone inhibited the proliferation of T lymphocytes and interferes with the TLR mechanism which is different from estrogen's effect on B lymphocytes. In addition, testosterone did not influence the intestinal epithelial cell barriers, unlike estrogen [75]. When the testes were removed from male mice with type 1 diabetes, the sex differences in gut microbiota disappeared, confirming the effect of androgens on gut microbiota [55].

22.3.1.2.2 Changes in the Gut Microbiota Due to Excess Androgen in Polycystic Ovary Syndrome

PCOS is a disease in which numerous ovarian cysts reduce normal ovarian tissue that secrete estrogen and increase blood androgen levels. In disease models of PCOS, there have been many reports about changes in the gut microbiota [73]. For example, in PCOS models with a high-fat diet and 5-alpha-DHT treatment, diversity of the gut microbiota and Bacteroidetes decreased, resulting in disorders in the gut microbiota [81]. In a study with 33 patients with PCOS, the distribution of gut microbiota was clearly different compared to that of healthy controls who were not obese. *Bacteroides*, *Escherichia/Shigella*, and *Streptococcus* levels were higher in patients with PCOS. There was a negative association with ghrelin and positive associations with testosterone and body mass index. Levels of *Akkermansia*, Ruminococcaceae, body weight, sex hormones, and brain-gut peptides decreased [82]. In a comparative study with eight obese patients with PCOS, 10 non-obese patients with PCOS, and nine controls, the PCOS groups had lower α-diversity and higher β-diversity [82]. Butyrate levels were only low in non-obese patients with PCOS, indicating that obesity is an important factor in gut microbiota disorders in patients with PCOS [83]. Fifty-eight obese adolescents with PCOS had lower α-diversity, higher Actinobacteria, lower Bacteroidetes, and similar levels of Firmicutes and Proteobacteria compared to controls [84]. Low α-diversity was closely related to high testosterone [85]. When letrozole, an aromatase antagonist that lowers androgen levels, was injected into PCOS-induced mice, reproduction, metabolism, and disorders in the

gut microbiota improved. When letrozole was withdrawn, the three factors reversed to similar levels as before, suggesting that symptom improvement is possible in patients with PCOS who maintain low androgen levels [86].

22.4 Conclusions

The gut microbiome is influenced by diet, ethnicity, age, antibiotics, stress, psychological factors, health of pregnant mothers, delivery methods (i.e., vaginal birth or cesarean section), environmental factors, and exercise. With the recent increase in the number of studies reporting sex differences in the gut microbiota, the role of sex hormones such as estrogen and androgen has been emphasized. For example, the composition of the gut microbiota before and after menopause is different, and the ratio of Firmicutes to Bacteroidetes increases after menopause to a level higher than that of males. There are differences in the gut microbiota according to stages of pregnancy, when changes in sex hormones are clear. In the T3, when estrogen levels are highest, α-diversity decreases. Moreover, there are sex differences in the effect of the vaginal bacteria of mothers on the gut microbiota and brain development of newborns. Male children are more strongly affected by maternal stress than female children. ERβ directly controls the metabolism of the gut microbiota, which in turn are actively involved in the metabolism of estrogen. β-glucuronidase in the gut microbiota mutates conjugated estrogen into its deconjugated forms, which enter into the enterohepatic circulation and act on the ERα and ERβ. This phenomenon does not occur before menopause in females, suggesting that it is limited to non-ovarian estrogen. In recent research, an association between sex hormones and the gut microbiota was shown by the observations that obese-type PCOS, by which blood androgen levels increase, causes disorders in gut microbiota and that treatment with letrozole, which is an aromatase antagonist that lowers the level of androgen, erases the changes in gut microbiota. Many diseases have been shown to be related to the gut microbiota, which are closely related to sex hormones. Therefore, research on differences in the gut microbiota related to sex hormones can aid in the development of new drugs.

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Gut Microbiota and Depression, Anxiety, and Cognitive Disorders

23

Hyun Jung Hur and Hye Youn Park

23.1 Introduction

It is widely accepted that the gut microbiome plays a crucial role in brain development and function in all types of animals, including human beings. In particular, the concept of *brain–gut–microbiome axis* explains the effect of gut microbiome on the development and function of the human brain [1]. A stream of research has found evidence supporting the bidirectional relationship between the gut microbiome and the brain through neurological, immunological, and metabolic pathways [1]. Specifically, the gut microbiome and bacterial flora can influence the cognition, emotion, and behaviors of organisms through these pathways. Concurrently, changes in the brain owing to stress or different emotions can influence the environment of the gut microbiota. Multiple epidemiological studies have pointed out the clinical comorbidity between psychiatric disorders and gastrointestinal symptoms and that psychological conditions such as depression and anxiety commonly coexist with functional dyspepsia and irritable bowel syndrome (IBS) [2]. Furthermore, researchers have suggested the existence of sex differences in the development and function of the brain–gut–microbiome system with sex hormones partially responsible for its development [3] (Fig. 23.1). Thus, this chapter discusses and elucidates the bidirectional relationship between the gut microbiome and brain function, specifically focusing on associations of the gut microbiome with depression, anxiety, and cognitive function, including sex differences in these associations.

23.2 Microbiome and Brain Functions

23.2.1 Bidirectional Relationship Between the Gut Microbiome and Brain Functions and Its Mechanism

A large number of animal studies have demonstrated that the gut microbiota can affect brain development and brain formation [4]. In particular, these studies have reported that transgenic and knockout mice lacking gut microbiota exhibit cognitive impairment caused by an underdevelopment of the hypothalamus–pituitary–adrenal (HPA) axis and a malformation of the hippocampus [5]. Many studies have also found out that abnormal behaviors such as excessive risky behaviors of mice are substantially reduced after normalizing their bacterial flora in intestines [6]. Regarding these changes in emotion and behavior, several studies have suggested that gut microbiota contribute to the manifestation of serotonin

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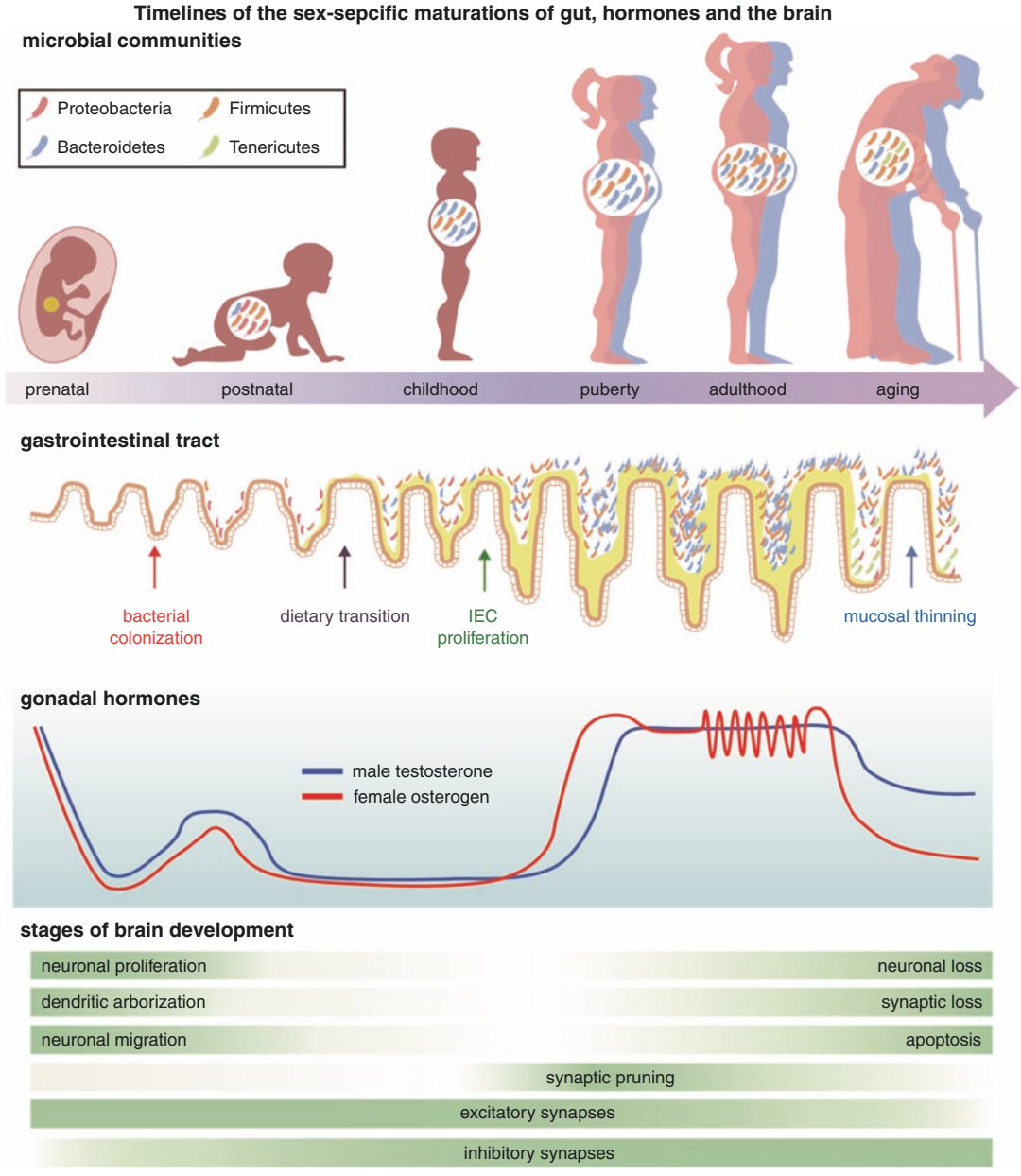

Fig. 23.1 Timelines of sex-specific maturations of gut, hormones, and the brain. *ICE* intestinal epithelial cell (adapted from Jašarević et al. [3])

(5-hydroxytryptamine) receptor and brain-derived neurotrophic factor (BDNF) in the brain [1].

In adulthood, as brain development is expected to be complete, the condition of gut microbiota remains stable. However, many factors such as changes in diet, antibiotic use, and stress may cause fluctuations in the intestinal environment [7]. For instance, when mice were given abundant taurine, changes in gut microbiota were observed [8]. Subsequently, their anxiety behaviors were reduced and cognitive learning was improved [8]. This finding implied that changes in gut microbiota can influence brain function and behaviors. Another study has illustrated that

changes in gut microbiome due to antibiotic intake can influence BDNF levels in the hippocampus and amygdala of mice [9]. Other studies have reported that low metabolite activities of dopamine and serotonin and BDNF expression in the hippocampus can be normalized by supplementing mice with a specific strain of probiotics that can prevent cognitive impairment due to stress [5, 10]. These results are in line with clinical findings that patients with IBS and patients who use antibiotics frequently show emotional and behavioral changes [11]. In other words, the gut microbiota play a major role in controlling multiple types of brain functions, including cognition, behavior, and emotion in organisms across their lifespans.

The gut microbiota can control brain function through various pathways. First, the neural pathway, which is mediated by the vagus nerve and gamma aminobutyric acid (GABA), is known to affect the level of anxiety or anxiety behavior [12]. The metabolic pathway comprises the second type of pathway, which can be demonstrated, for instance, by the metabolism of tryptophan in organisms, which can influence emotions such as depression by changing serotonin activity [13]. Gut microbiota are involved in moderating levels of cytokines and their secretion through the immunological pathway in the intestine or the entire body [14]. For example, the association between antibiotic or probiotic use and changes in depressive symptoms can be explained by the fact that the gut microbiota can influence the modulation of cytokines such as interleukin-4 (IL-4) and interferon-gamma (IFN-gamma) related to the pathophysiology of depression [15]. The last type of pathway that can control brain function is the digestive pathway. As a giant endocrine organ, the digestive system can modulate the secretion of gastrin, cholecystokinin, and serotonin, which in turn can make changes in endocrine cells and alter multiple peptides related to brain function [16]. Apart from these pathways, several recent studies have hypothesized the existence of other direct neuroregulating mechanisms because neurotransmitters such as noradrenaline, dopamine, and acetylcholine can be extracted from bacteria. These studies suggest that the use of probiotics is an alternative treatment for psychiatric conditions [17].

On the contrary, changes in the brain can influence the constitution of gut microbiota. Many experiments have illustrated that excessive stress can alter gut microbiota in mice [18]. Many studies have found that noradrenaline, which is increased during high levels of stress, may alter gene expression of certain bacteria [19]. Although specific mechanisms of this finding are only partially established, this stream of study has investigated the effect of changes in brain function on gut microbiota and its environment and emphasized the importance of further studies in this area.

23.2.2 Sex Differences Related to Gut Microbiota and Brain Function

Several researchers have observed sex differences in the development and maintenance of the brain–gut–microbiome axis [3]. This difference ranges from the prenatal period to old age. Moreover, from a clinical point of view, the incidence rate, severity, and treatment outcomes of certain diseases are closely related to sex differences [3]. Taking IBS as an example, this type of functional gastrointestinal disorder is more common in women. Physiological changes in the intestine due to sex hormones can explain this sex difference [20]. Moreover, sex differences can be observed even during the prenatal period. At this stage, the mother's microbial environment can influence sex-specific and neural development of the fetus [21]. Recent experiments on mice have revealed that psychological stress of the mother can lead to reduced levels of *Lactobacillus* in newborn mice and that environmental changes in gut microbiota exhibit differences dependent on the sex of newborn mice [22]. At puberty, this sex difference becomes more distinct. In particular, testosterone, the male sex hormone, is recognized as a factor that can induce changes in gut microbiota and lead to distinct differences between men and women. Such difference can last throughout adulthood [23].

During adulthood, sex difference in the gut microbiome remains steady. Some epidemiological studies in Europe have demonstrated that adult males display significantly increased levels of gut microbiota, including *Bacteriodes* and *Prevotella*, than adult females [24]. Moreover, females are relatively prone to fluctuations in gut microbiome due to changes in female sex hormones caused by pregnancy, childbirth, and menopause [23]. In particular, researchers have pointed out that levels of ovarian hormones are decreased in women undergoing menopause, which is closely related to the onset or exacerbation of depression, anxiety, and gastrointestinal symptoms. This notion supports the link of gut microbiota to sex hormones and brain function [20, 25].

In late adulthood, numerous changes occur in gut microbiota and brain function. In general, the digestive system becomes weak, the diversity of the gut microbiome diminishes, the intestinal wall dysfunctions, and inflammatory responses increase [26]. Specifically, research has suggested that changes in gut microbiome can mediate reduced levels of female sex hormones, depression, and cognitive impairment [27]. However, the detailed mechanism of this relationship remains unknown, which requires further studies.

23.3 Gut Microbiome, Depression, and Anxiety

Gut microbiota are associated with the onset and progress of psychiatric disorders, especially depression and anxiety [28]. Previous studies have argued that patients with major depressive disorder (MDD) exhibit significantly different compositions of fecal microbiota compared with healthy controls [28, 29]. In particular, a few studies have reported that the severity of depression is related to increased levels of Enterobacteriaceae and *Allistipes* and decreased levels of *Faecalibacterium* [29]. Similarly, observational studies have indicated that the number of specific genera in gut microbiota, such as *Faecalibacterium*, *Eubacterium rectale*, *Lachnospira*, *Butyricicoccus*, and *Sutterella*, is decreased in patients with generalized anxiety disorder (GAD) [30]. Stress-related pathways such as the HPA axis play a crucial role in the etiological mechanism of depression and anxiety. It has been suggested that the gut microbiome can influence the development and function of this pathway [31]. In experiments on animals, germ-free mice without gut microbiota display reactions that are different from those of control mice with a gut microbiome. Specifically, germ-free mice showed an excessively activated HPA axis or remarkably different activation levels of norepinephrine, dopamine, and serotonin [32]. Additionally, the immune system of germ-free mice tended to develop abnormally, making them vulnerable to systemic infection, neuroinflammation, and consequent presentations of abnormal behaviors [33].

23.3.1 Association of the Gut Microbiome with Depression or Anxiety

The inflammatory immune response is involved with the onset and progress of depression and anxiety. Research studies on patients with depression have found that levels of proinflammatory cytokines are increased [34] and depressive symptoms are improved after administration of antibiotics [35]. These results were replicated in a study on patients with anxiety disorder by demonstrating that patients with anxiety disorders displayed increased levels of proinflammatory cytokines [36]. Similarly, an animal study on anxiety-modeled mice has suggested that IL-6, a proinflammatory cytokine, is closely related to anxiety behaviors of mice [37]. The gut microbiome directly and indirectly affects immunological and pathophysiological mechanisms of depression and anxiety by controlling functions of the epithelial wall, immune system, and autonomic nerve in the gut [1] (Fig. 23.2). In addition, gut microbiota can reduce stress-induced endotoxemia and neuroinflammation by maintaining the function of the intestinal wall and facilitating anti-inflammatory reactions of immu-

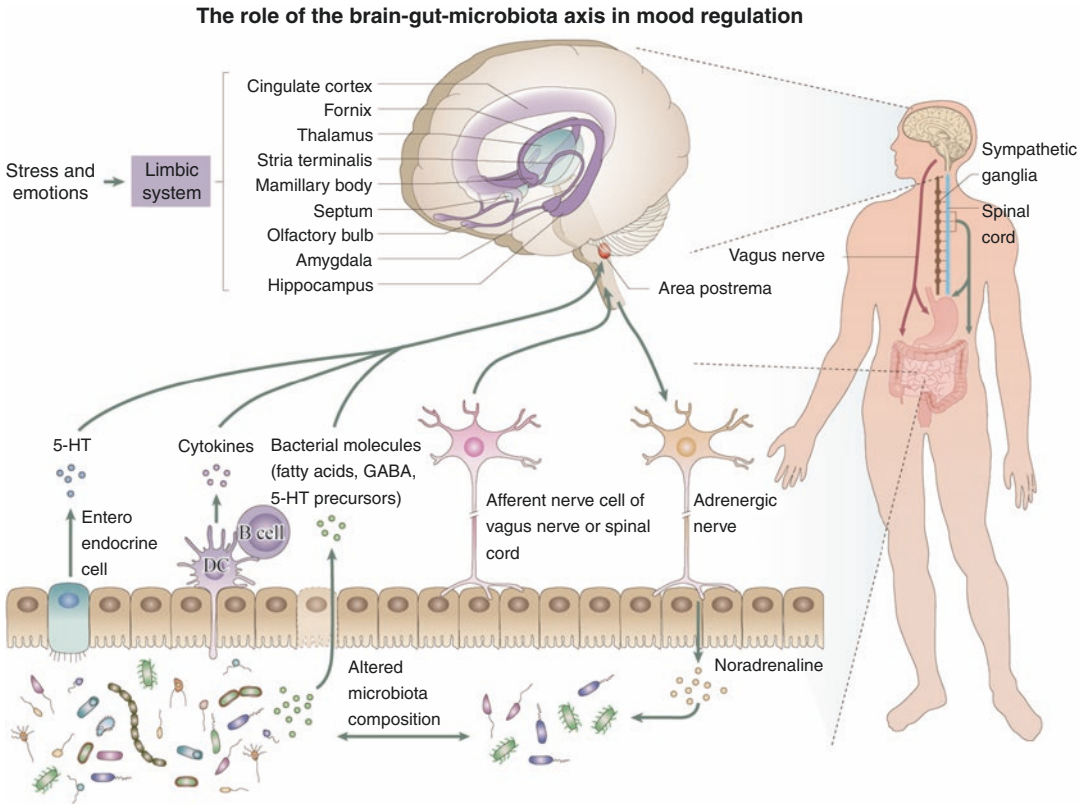

Fig. 23.2 The role of the brain-gut-microbiota axis in mood regulation. *DC* dendritic cell, *GABA* γ-aminobutyric acid, *5-HT* 5-hydroxytryptamine (adapted from Collins et al. [1])

nocytes. Thus, gut microbiota ultimately contribute to the modulation of depression and anxiety symptoms related to neuroinflammation [38].

Gut microbiota are also involved in the production of short-chain fatty acids (SCFAs) during the metabolism of carbohydrates. As SCFAs facilitate the division of T-cells in the immune system and the generation of neurotransmitters, the reduction or dysfunction of microbiota in the intestine can decrease SCFA metabolism, which can partially explain the relationship between changes in the gut microbiome and depression [39]. Moreover, the gut microbiome is partially involved in synthesizing precursors of major neurotransmitters related to depression, such as GABA, serotonin, norepinephrine, and dopamine. In this regard, many studies have offered evidence that patients with MDD display decreased levels of *Bifidobacterium*, which is necessary for GABA synthesis [40].

Another possible mechanism that the gut microbiome influences depression and anxiety is through the control of intestinal peptide secretion from enteroendocrine cells mediated by the brain–gut–microbiome axis, which regulates brain function. Several studies on animals have indicated that germ-free mice exhibit increased levels of neuropeptide Y, glucagon-like peptide, and ghrelin or decreased levels of cholecystokinin [41, 42]. The neuropeptide Y receptor is involved in GABA modulation, whereas the glucagon-like peptide, BDNF, and cholecystokinin receptors are involved in the modulation of GABA, glutamate, dopamine, and acetylcholine. As a result, researchers have suggested that these mechanisms can mediate the activation of the brain–gut–microbiome axis and the gut–brain signaling system. They have also suggested that changes in the gut microbiome can influence the development or remission of depression and anx-

iety behaviors [39]. Many findings support this notion by demonstrating that the use of antibiotics can lead to alterations in the microbiome, disrupted intestinal homeostasis, and increased risk of depression [43]. Recently, studies on animals have reported that certain probiotics can exert anxiolytic effects by stimulating the vagus nerve, suggesting the possible involvement of gut microbiome in the control of the vagus nerve [44]. However, additional studies and investigations regarding this mechanism are required. Recent studies on patients with depression have also observed significant differences in several types of gut microbiome (i.e., Bacteroidetes, Firmicutes, Actinobacteria, Fusobacteria, and Proteobacteria). However, results of these studies are mixed on whether the level of specific gut microbiome is increased or decreased, leading to a lack of consensus on which gut microbiome is directly related to depression [39]. Thus, future studies should investigate this area using methods that are more systematic considering other factors, such as comorbidity of psychiatric disorders, other medical conditions, drug effects, and standardized measurements.

In terms of using probiotics as a treatment, many animal studies have indicated that the hyperactivity of the HPA axis could be relieved and that cortisol levels could be diminished using probiotics [12, 45]. Another study with healthy subjects has also demonstrated an alleviation of increased levels of stress-induced cortisol [46]. These results confirm that the gut microbiome could control stress reaction. As illustrated by several studies, abnormal behaviors in mice with depressive and anxiety symptoms are reduced after the administration of probiotics [47]. These probiotics are also effective in relieving depressive mood or stress in humans [48, 49]. However, studies focusing on probiotic treatment for patients with depression or anxiety disorders remain limited with mixed results depending on the strain used in the research or the population of subjects [39]. Thus, follow-up studies on probiotic treatment are needed. A few studies have demonstrated that several antidepressants could relieve depressive symptoms in patients with depression by modifying gut microbiome dysbiosis through antimicrobial effects. However, supporting evidence remains limited [50].

23.3.2 Sex Difference Related to Gut Microbiome, Depression, and Anxiety and Its Mechanism

Depression and anxiety are more common in women than in men. Factors such as sex hormones, differences in the gut microbiome and immune system, and reactivity to stress contribute to such difference in terms of psychiatric disorders [51, 52]. Although androgen (male sex hormone) tends to exert antianxiety effects, low levels of estrogen (female sex hormone) are related to increased risk for depression because estrogen activates the brain–gut–microbiome axis [53, 54] and acts as an anti-inflammatory agent of neuroinflammation [51, 55]. It has been reported that microglia contribute to this neuroimmunological sex difference. Microglia are major immunocytes in the central nervous system with main roles in the secretion of cytokines and function of macrophages. Sex differences in terms of microglia can be observed in early stages of human development. For instance, microglia are more activated in men than in women, and estrogen and testosterone differently influence the anti-inflammatory function of microglia [55]. These sex differences in the manifestation and maturation of microglia can partially explain the mechanisms of different vulnerabilities to depression and anxiety between men and women, with microbiome influencing the onset or progress of depression and anxiety by involving the manifestation and function of the microglia [55].

Sex hormones can control inflammatory reaction and brain function by mediating the gut microbiome. Many studies support this notion by illustrating that women tend to have fewer Bacteroidetes than men. This low level of Bacteroidetes is related to clinical depression [56]. Recent research has suggested that sex difference in terms of gut microbiota might

exist as a depression-related biomarker [57]. Moreover, other studies have confirmed that the number of Actinobacteria is increased in female patients with depression, whereas the number of Bacteroidetes is relatively decreased in male patients with depression compared to that in a healthy group [57]. Another study has observed an increase in inflammatory reaction and intestinal permeability due to stress only in women but not in men, which could contribute to the sex difference in gut microbiome [58]. Nevertheless, this biological mechanism contributes to the fact that women are more vulnerable to depression and anxiety than men in addition to other factors, such as interpersonal relationships, manifestation of symptoms, obesity, levels of activity, and social roles. To gain further knowledge regarding the effect of gut microbiome on sex differences related to depression and anxiety, additional studies that employ specific and sophisticated designs are required.

23.4 Gut Microbiome and Cognitive Function

For a long time, researchers have widely recognized that the gut microbiome is associated with multiple cognitive functions such as attention, memory, and learning. Several animal studies have reported that differences or changes in the gut microbiome can specifically influence memory and learning and that antibiotic use can lead to learning impairment in germ-free mice [59]. On the contrary, when probiotics are given, germ-free mice displayed improvements in cognitive tasks and BDNF levels [60, 61]. These results were replicated in human studies. It has been found that obesity affects gut microbiome which links to brain microstructures and cognitive functions [62]. Moreover, the diversity of the gut microbiome is significantly reduced in patients with Alzheimer's disease than in patients with mild cognitive impairment or healthy controls [63]

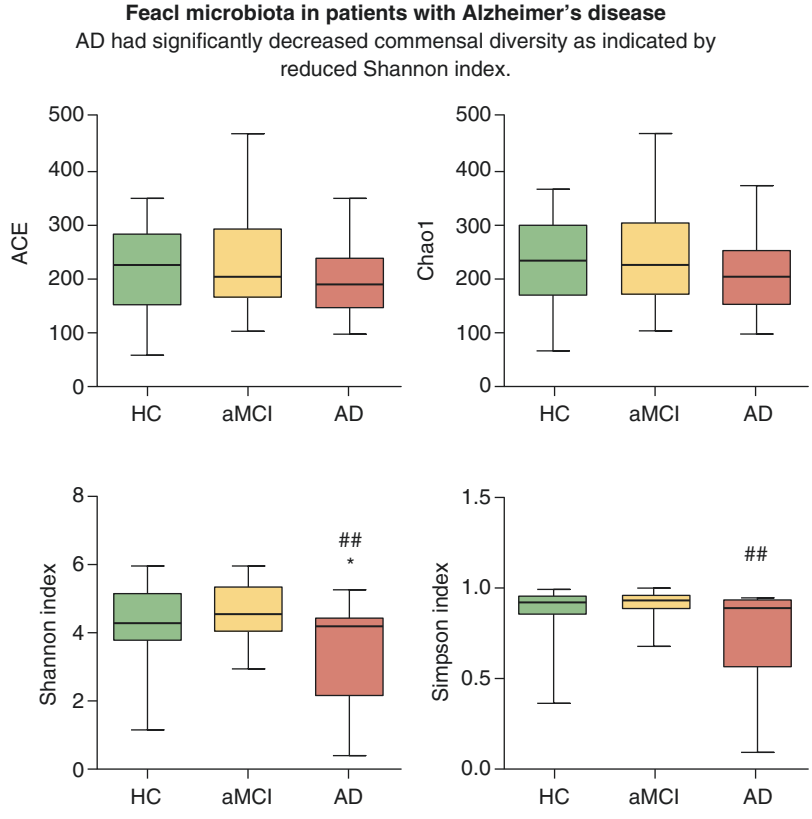

Fig. 23.3 Fecal microbiota in patients with Alzheimer's disease. The α-diversity of the fecal microbiome among three groups is depicted according to ACE, Chao 1, Shannon index and Simpson index. *HC* normal cognition healthy control, *aMCI* amnestic mild cognitive impairment, *AD* Alzheimer's disease (adapted from Liu et al. [63])

(Fig. 23.3). Many studies have indicated that memory including working memory is improved in the elderly after probiotic use [64]. However, results are relatively confusing [65]. They remain inconclusive as mechanisms regarding the gut microbiome and cognitive functions are not well understood. Many researchers have proposed that the gut microbiome is a protective factor for stress or inflammatory reaction that could lead to cognitive impairment [66].

23.4.1 Gut Microbiome and Cognitive Impairment

Aging can lead to alteration in the gut microbiome. Reduced diversity of the gut microbiome is closely related to frailty and cognitive impairment in the elderly [67]. Alzheimer's disease is a neurodegenerative disease whose major symptoms include cognitive impairment. Many studies have examined the role of gut microbiome in cognitive functions and provided evidence for

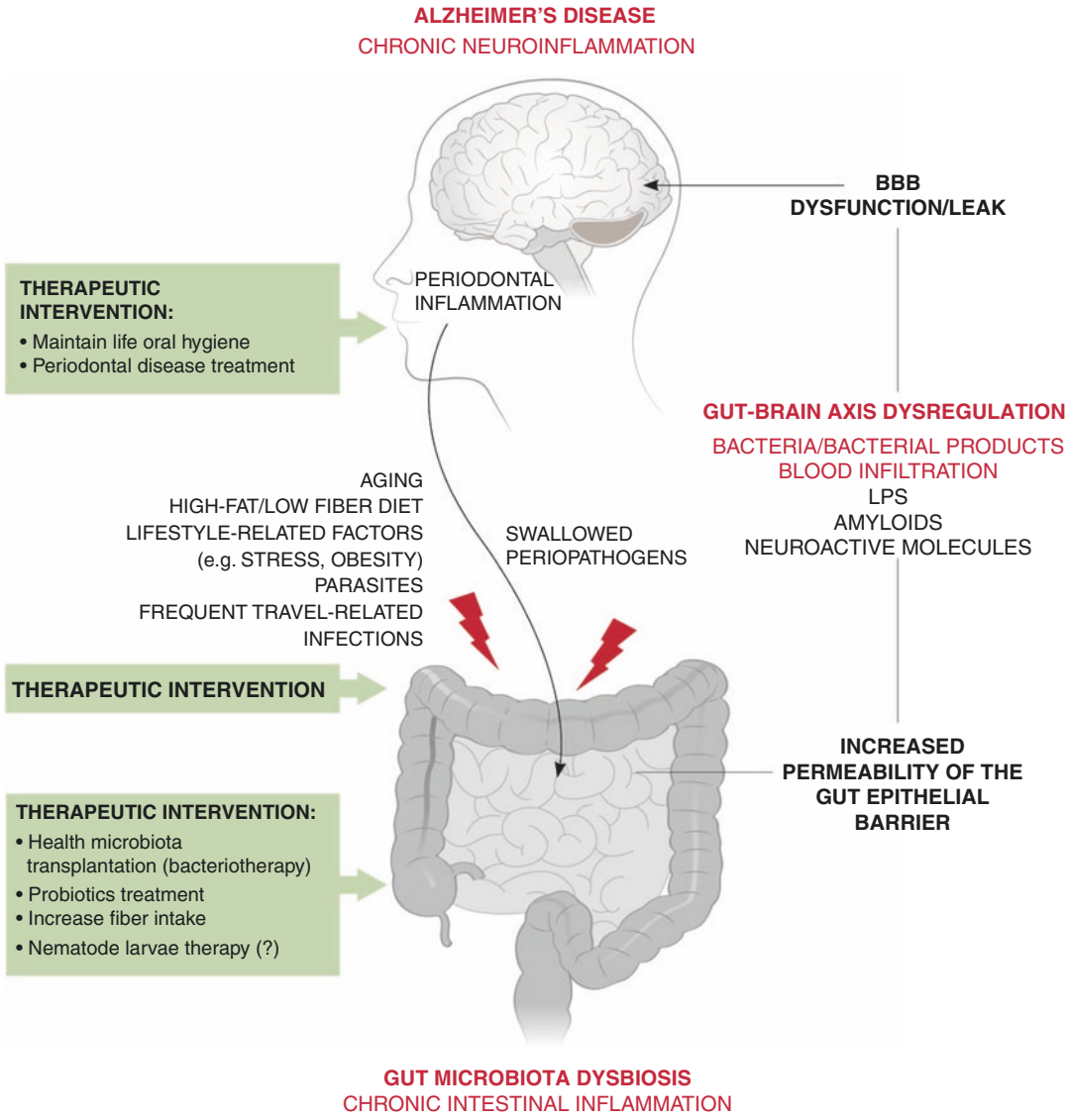

Fig. 23.4 Gut microbiota dysbiosis and Alzheimer's disease: mechanisms and therapeutic implications. *BBB* blood-brain barrier, *LPS* Lipopolysaccharide (adapted from Sochocka et al. [68])

the association between gut microbiome and cognitive function [68] (Fig. 23.4). The main cause of Alzheimer's disease is the accumulation of amyloid-beta and tau protein [68]. Specifically, the accumulation of beta-amyloid protein can activate microglia and induce inflammatory responses in the brain. Beta-amyloid can be removed through immune reaction in the acute phase. However, aging leads to changes in the immune system, which enables continued microglia activation and results in chronic inflammation that can induce neurotoxin and, ultimately, brain damage [69]. During this process, astrocytes also become activated. Activated astrocytes lead to augmentation of neuroinflammation and dysfunction in the blood–brain barrier (BBB), which could escalate degeneration and neural damage [69]. As previously cited, the gut microbiome plays a crucial role in systemic and neural immune systems and controls several neurotransmitters such as serotonin, melatonin, GABA, and acetylcholine. For this reason, many studies have pointed out that the altered gut microbiome promotes the development of neurodegenerative diseases such as Alzheimer's disease by controlling neural inflammation through changes in microglia, BBB, and systemic inflammatory reaction [68]. Many studies have found changes in *Bacteroides vulgatus* and *Campylobacter jejuni* known to influence glutamate metabolism in patients with dementia [70]. Additionally, recent animal studies have reported that probiotic use or fecal transplantation could control the gut microbiome by reducing neurotoxins such as beta-amyloid and neural inflammatory response [71, 72]. By contrast, a recent systematic review of randomized controlled trials that administered probiotics to patients with Alzheimer's disease demonstrated no significant effect of probiotics on cognitive functions of patients [73]. In other words, changes in the intestinal environment of gut microbiome are directly related to aging in terms of cognitive function and impairment. However, a detailed mechanism of how the intestinal immune reaction improves cognitive impairment through diet change or probiotic use requires a thorough examination.

23.4.2 Sex Difference Related to Gut Microbiome and Cognitive Impairment and Its Mechanism

As Alzheimer's disease is common for women than for men, the previous studies infer that sex differences may exist in the etiological mechanism [74]. First, sex differences may occur in the function of the gut microbiome regarding the accumulation of beta-amyloid, which is a crucial etiological mechanism of Alzheimer's disease. A series of research studies have indicated sex differences in the accumulation of beta-amyloid. These studies found that the gut microbiome could mediate the relationship between calorie-limit diet and beta-amyloid accumulation [75, 76]. According to a study conducted on mice, limited carbohydrate intake could reduce beta-amyloid buildup in female but not male mice [76]. Moreover, sex differences in the mechanism of microglia functions and genetic expression were observed [77] (Fig. 23.5). For example, Minter et al. [78] have observed that when mice are administered with antibiotics, their gut microbiome is changed, leading to reductions in microglia and astrocytes. However, this finding is applicable to male mice only. This sex difference can be regarded as a function of the gut microbiome in terms of modulating sex hormones. Other studies have demonstrated that administrating sex hormones can cause changes in the gut microbiome [9], whereas several studies have proposed that the microbiome in the intestine could lead to changes in metabolism and levels of sex hormones such as androgen and estrogen [79]. In this manner, the specific mechanism regarding the association between gut microbiome and neurodegenerative disorders and its sex difference are only partially established. Numerous studies have provided evidence that further research is needed in this area considering sex-specific factors as possible mechanisms.

23.5 Conclusions

The gut microbiome is one of crucial factors that influence brain development and function. It plays a role in modulating cognition, emotion,

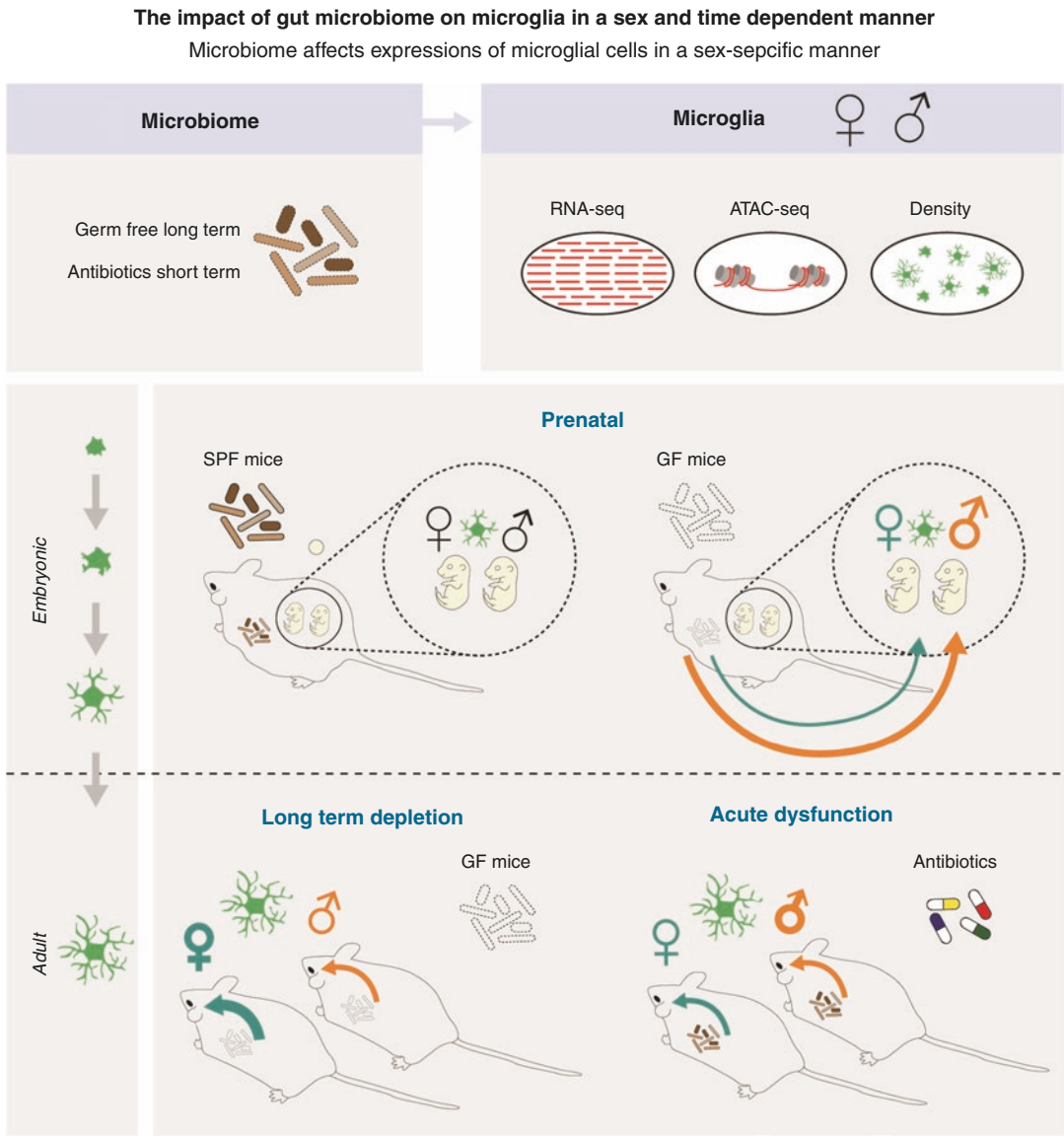

Fig. 23.5 The impact of gut microbiome on microglia in a sex- and time-dependent manner. Microbiome affects expressions of microglial cells in a sex-specific manner. *SPF* specific-pathogen free, *GF* germ-free (adapted from Thion et al. [77])

and behavior through various pathways. The major pathway is the neural pathway, which regulates depressive and anxiety symptoms through the metabolism process of neurotransmitters such as serotonin, noradrenaline, and GABA. Furthermore, this pathway regulates the parasympathetic nerve. In this pathway, gut microbiota can affect the onset of depression, the progress of depression, and anxiety by triggering regulatory stress reactions and systemic immune responses. Many studies have suggested that probiotic intake could relieve depressive and anxiety symptoms. However, evidence to substantiate this claim remains limited and requires further investigation. Depression and anxiety disorders are more common in women in men. Symptoms

and progress of these psychiatric disorders need to consider sex differences, which could partially explain the modulation of sex hormones and anti-inflammatory reaction depending on sex. Gut microbiota can influence cognitive function, whereas a decreased number of microorganisms in the gut microbiome is closely related to impairment in domains of attention, memory, and learning. As suggested by a few studies, the accumulation of beta-amyloid and increased microglia, which are main causes of dementia such as in Alzheimer's disease, are associated with the gut microbiome. The abovementioned studies have offered evidence of a neuroinflammation-controlling mechanism of gut microbiota in the development of neurocognitive disorders. Moreover, these studies have pointed out sex differences in the development of dementia, which the gut microbiome plays a partial role by regulating sex hormones and neural damage or neurodegenerative process.

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24 Sex Differences and Gut Microbiota Changes in Parkinson's Disease

Jee Young Lee and Cheol Min Shin

24.1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting hundreds of individuals per 100,000 population, and the prevalence increases up to 5% in population above 80 years old. The pathological hallmark is neuronal loss with Lewy bodies containing phosphorylated alpha-synuclein aggregates. Brain pathology can appear in the focal regions in the olfactory bulb or the lower medulla, but it ultimately propagates into the widespread subcortical and cortical areas in the brain. Particular involvement of the substantia nigra results in degeneration of dopaminergic neurons which is responsible for typical clinical symptoms of PD: rigidity, tremor, bradykinesia, and postural instability.

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Sex differences are reported in many aspects of PD including epidemiology, clinical features, and genetic or biomarkers. However, the most interesting part comes from the discovery that gut is one of the peripheral organs with α-synuclein pathology preceding the central nervous system involvement in PD, and inflammation in the gut can affect pathological α-synuclein spreading through the brain, which highlights the gut-brain axis in the pathogenesis of PD. Furthermore, GI disorders are observed in about two-thirds of PD patients [1], contributed by the α-synuclein pathology in the gut and vagal nucleus, as well as chronic dopaminergic drug intakes, and other nutritional or dietary problems. Therefore, pathophysiological research on the gut pathology and GI dysfunctions in PD patients would provide a valuable clue to revealing the pathogenesis of PD. Sex hormone is known to affect gut permeability and various aspects of GI disorders; thus, the sex-specific alterations in the gut-brain axis gather increasing attention more than ever before with increasing knowledge on the gut functions and the role of microbiome in humans.

In this chapter, we will review the literatures addressing sex differences in PD and the role of gut microbiome in the pathogenesis of PD. Then, we will finally discuss whether the sex-specific gut microbiome changes could be linked to the sex-different mechanism for both the pathogenesis and clinical features of PD.

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24.2 Sex Difference in Parkinson's Disease

24.2.1 Epidemiological Risk Factors Differently Affecting Men and Women

Many studies consistently reported that males are more affected than females by approximately two-fold. The sex difference is more evident in sporadic PD than young-onset PD patients, who are more affected by genetic predisposition. However, Korean studies have not shown the male preponderance in PD, and the female to male ratio is above 1 in most Korean cohort studies. Japanese epidemiology study also showed female predominance in PD [2]. The disparity might be due to the specific feature of the elderly population in these countries, and unknown genetic or cultural/environmental factors controverting the potential protective effect of estrogen. Elderly females in Korea might be more exposed to risk factors of PD than males, for example, no-smoking, no alcohol consumption, pesticide exposure, head trauma, agricultural occupation, dietary deficiency, and well-water drinking. Nevertheless, this hypothesis has not been proven. Interestingly, male predominance is observed in young-onset PD in a recent Korean epidemiology study [3].

We also observed sex differences in PD risk predicted by smoking, alcohol, and serum ɣ-glutamyl transferase levels in the Korean population [4, 5]. Studies also reported sex-different impacts of urate [6], and cholesterol levels in the statin-free cohort [7]. All these studies show that the most robustly demonstrated epidemiologic risk factors of PD seem to play a role in men but not in women.

The negative impact of high urate levels on the development of PD is significantly demonstrated in *LRRK2* mutation carriers, especially for women [8]. *LRRK2* (the gene encoding leucine-rich repeat kinase 2) is the most common genetic cause of PD, and among the *LRRK2* carriers, PD relatively equally affects both men and women [9]. The sex-different predisposition is also observed with GBA-associated parkinsonism. *GBA1* is the gene encoding the lysosomal enzyme glucocerebrosidase (GCase) and is one of the important genetic causes which highlight the pathogenic role of lysosomal dysfunction and resultant reduced alpha-synuclein degradation, thus contributing to the development of PD [10]. Among the GBA carriers, galactosidase alpha (GLA) activity, encoded by a gene on the X chromosome, is linked to PD [11].

24.2.2 Specific Clinical Features Predicted by Biological Sex in Parkinson's Disease

From the aspects of clinical phenotype, PD is a highly heterogeneous disorder [12]. The traditional classification is the tremor-dominant with benign disease type and the postural instability-gait disorder with malignant disease type. The latter type is linked to earlier dementia and autonomic dysfunction. However, many PD patients do not fit into this classification, and recently, there are many intermediate and sequestered phenotypes reported so far based on the data-driven analysis from the large multicenter longitudinal databases containing clinical, neuroimaging, and body-fluid biomarker information, such as Parkinson's Progression Markers Initiative (PPMI) study (https://www.ppmi-info.org). There is no study showing apparent differences in the distribution of these phenotypes between the sexes, but female sex can predict some clinical features. Females tend to show milder rigidity, more tremor, and a higher propensity to develop postural instability and an elevated risk for levodopa-related motor complications during the disease course [13–15], although many other factors especially disease duration and severity and regimens of dopaminergic medications should also be considered in clinical practice. Of note, camptocormia, a skeletal abnormality with forward-flexion of the trunk, is more frequently observed in male than female patients. An ongoing clinical trial evaluates the sex-different prevalence of various skeletal abnormalities in parkinsonism such as camptocormia, Pisa syndrome, antecollis, scoliosis, and striatal hand or toe (clinicaltrial.gov. NCT03573232).

Cognitive functions are differently predicted by biological sex in PD. Male patients are more likely to have executive dysfunction and impaired facial emotion recognition while female patients do with visuospatial dysfunction [16, 17]. Some nonmotor symptoms such as anxiety, depression, constipation, and pain are particularly observed in female patients [18–20].

24.2.3 Hypothesized Mechanisms for Sex Differences in Parkinson's Disease Pathogenesis

The distinctive clinical features and risk factors between males and females may be associated with estrogen. Recently, numerous studies have reported different functional networks and pattern of gray and white matter atrophies between men and women, suggesting that neuroimaging analysis should consider biological sex as an essential confounding variable [21].

Regarding dopaminergic neuronal degeneration in the substantia nigra, studies have shown sex-different genetic expressions in human dopaminergic neurons. Males have upregulated genes, such as *SNCA* and *PINK1* [22], and downregulated transcriptions related to oxidative stress, apoptosis, and synaptic and axonal transmission [23]. Gene products for metabolic processes and mitochondrial energy consumption are generally upregulated in males compared to females [23]. This gene-level expression of dopaminergic neurons in men points towards a predisposition to neurodegeneration of male gender. The development of D1 and D2 receptor systems in the human brain differs by sex, and after grown-up, males have heightened D2:D1 receptor ratios in all brain regions than females [24]. These heterogeneous dopamine receptor densities between sexes might explain the clinical features of female PD patients of later motor symptom development and more frequent levodopa-induced dyskinesias than the male counterpart. It is also known that estradiol increases the synthesis, release, reuptake, and turnover of dopamine [25], which is linked to a predisposition of females to adverse levodopa-induced motor behaviors.

Neuroinflammation is one of the key pathophysiological mechanisms of neurodegeneration in PD, of which microglia and astrocytes are key actors. It is known that microglial maturation and immunity are sex-specifically developed in the human brain [26]. Animal PD model studies have shown that estrogen could attenuate microglial activation and enhance microglia polarization directed toward a more cytoprotective phenotype [27]. Bioenergetic properties of astrocytes in the physiological oxygen tension, like the environment inside the brain, are also shown to differ by biological sex [28]. However, whether the astrocytes' actions differently affect the development of PD by biological sex has not been revealed.

The tolerability to oxidative stress of neurons is thought to be different between males and females. Higher mitochondrial respiratory chain activity and lower calcium uptake capacity [29–31], bigger neuromelanin volume in the substantia nigra [32], and greater resistance to iron-mediated oxidative stress [33, 34] have been demonstrated in females than males by experimental studies. However, how exactly these sex-different properties affect the development of Lewy body pathologies in the brain has not been specifically investigated.

24.2.4 Gastrointestinal Symptoms in Parkinson's Disease Patients Reflect the Different Influence on Dysmotility by Biological Sex

Constipation is reported to be more common in females than male PD patients by a cohort study surveying nonmotor symptoms of 951 PD patients [35]. However, few studies prospectively investigate dysmotility symptoms both relating to the upper and lower GI tracts. There was a randomized controlled trial specifically targeting GI dysfunctions as a primary outcome in PD patients in Korea [36]. This multicenter trial evaluated GI symptoms of participants before and 4 weeks after DA-9701 therapy compared with placebo treatment, and further evaluated symptom changes after additional 8 weeks of DA-9701

therapy in both treated groups. We conducted the subgroup analysis using the clinical trial database whether there is a sex difference in GI symptoms. We compared GI symptom severity between males and females assessed on the Korean Nepean dyspepsia index (NDI-K), GI symptom diary and Bristol stool scale in association with the severity and duration of PD, and anti-parkinsonian drug dosages using multiple linear regression models (Table 24.1). The NDI-K symptom and NDI-K QoL scores were both higher in female patients (13.62 vs. 22.28, and 47.33 vs. 58.37 in men and women, adjusted p = 0.007 and 0.001, respectively, by linear regression). Female patients complained of early fullness and bloating in the upper abdomen after a meal more frequently than males in their GI symptom diary. In Bristol stool scale and defecation frequency, constipation symptom was also worse in female patients. When we performed a

Table 24.1 Sex differences of gastrointestinal symptoms in PD patients who participated in the PASS-GI[a] clinical trial

	Men (n = 78, 54.2%)	Women (n = 66, 45.8%)	p-value[b]
NDI-K symptom score (total)	13.62 (10.41)	22.28 (23.34)	0.007
Dyspepsia sum score[c]	8.18 (6.48)	16.09 (16.19)	<0.001
GI symptom diary (per day)			
Inability to finish meals due to early fullness			0.001
Absent	50 (64.1)	29 (46.8)	
Once	21 (26.9)	11 (17.7)	
Twice	1 (1.3)	9 (14.5)	
Three times (every meal)	6 (7.7)	13 (21.0)	
Bloating in the upper abdomen after a meal			0.025
Absent	53 (67.9)	34 (54.8)	
Once	21 (26.9)	15 (24.2)	
Twice	3 (3.8)	5 (8.1)	
Three times (every meal)	1 (1.3)	8 (12.9)	
Burning or pain in the upper abdomen			0.146
Absent	60 (76.9)	40 (63.5)	
Mild	17 (21.8)	17 (27.0)	
Moderate	1 (1.3)	2 (3.2)	
Severe	0	3 (4.8)	
Very severe	0	1 (1.6)	
Bristol stool scale			0.001
Type 1 (severe constipation)	7 (9.1)	15 (23.4)	
Type 2	23 (29.9)	13 (20.3)	
Type 3, 4	45 (58.4)	25 (39.1)	
Type 5	1 (1.3)	8 (12.5)	
Type 6	0 (0)	3 (4.7)	
Type 7 (severe diarrhea)	1 (1.3)	0 (0)	
Defecation frequency (per day)			0.001
<1	16 (21.3)	24 (40.0)	
1	44 (58.7)	35 (58.3)	
>1	15 (20.0)	1 (1.7)	

[a]A multi-center double-blind randomized placebo-controlled trial of DA-9701 in the treatment of gastrointestinal symptoms in PD patients conducted in Korea [36]

[b]by multivariate logistic regression models controlling for age, disease duration, and PD severity assessed on the Unified PD Rating Scale

[c]Dyspepsia sum score comprises 8 items of the NDI-K scale: upper abdominal pain, discomfort, burning, pressure and bloating sensation, inability to finish a regular meal, fullness after eating, and nausea

post-hoc analysis of the NDI-K dyspepsia symptoms, pain in the upper abdomen, inability to finish regular meals, fullness after eating, and nausea were significantly worse in female patients (corrected $p < 0.05$ for all). This subgroup analysis result highlights the apparent sex differences in GI symptoms in PD patients. Among the dyspepsia symptoms, impaired gastric accommodation seems to be a predominant symptom in female PD patients, which requires further studies to confirm this dysfunctional symptom in female PD patients and address its pathophysiological mechanism.

24.3 Gut Microbiota Changes in Parkinson's Disease

The GI tract plays an important role in the pathophysiology of PD. Pathologically, Lewy bodies are observed not only in the substantia nigra, but also in non-dopaminergic neurons outside the basal ganglia [37]. α-synuclein deposition and neurodegeneration in the enteric nervous system are associated with the constipation in PD patients [38, 39]. Clinically, constipation may occur years before the onset of motor symptoms [40]. Vagotomy may reduce the risk of developing PD [41]. Therefore, it is reasonable to assume that the alternations of the gut environment may affect the development of PD [42–44].

The clinical picture of PD is strongly influenced by the gut microbiota. Gut microbes like *Bacillus* species can produce dopamine, and gut microbiota accounts for almost half of the dopamine production in human body [45, 46]. Gut microbiota affects the brain activity through microbiota-gut-brain axis under both healthy and disease conditions including PD [47–50]. Microbiota and the brain crosstalk *via* the immune system, tryptophan metabolism, and the vagus nerve and the enteric nervous system. Microbial metabolites such as short-chain fatty acids (SCFAs), branched chain amino acids, and peptidoglycans are involved in the communication [51].

It has been suggested that intestinal dysbiosis can promote the pathology of PD. First, small intestinal bacterial overgrowth (SIBO) has also been associated with PD [52–55]. In patients with PD, the presence of SIBO has been associated with a greater degree of motor impairment attributed to fluctuation in levodopa response [53]. In the α-synuclein overexpression mouse model, transplantation of fecal microbiota from PD patients leads to a significantly higher chance of developing symptoms of PD compared to transplanting fecal microbiota from healthy donors [56]. Chronic oral administration of rotenone has been reported to cause GI dysfunction and intestinal dysbiosis prior to the development of motor dysfunction and CNS pathology [57].

24.3.1 Gut Microbiota Signature in Parkinson's Disease

Gut dysbiosis is more prevalent in PD patients than in healthy controls. The compositions of both fecal and mucosal microorganisms have been reported to be different in PD patients 58–61]. However, care must be taken in interpreting microbiome changes in PD patients. For example, gut microbiota is substantially affected by the diet and the environment [58, 59]. Dietary habits may change after a diagnosis of PD. Especially, PD patients may increase fiber intake to improve GI symptoms such as constipation.

The results of previous studies on microbiota signature of PD patients are inconsistent. Nevertheless, some interesting findings are summarized as below. First, butyrate-producing bacteria were significantly decreased in fecal samples in PD patients [60]. One study reported that the cellulose-degrading bacteria such as *Blautia, Faecalibacterium*, and *Ruminococcus* were significantly decreased, whereas the pathobionts from *Escherichia*, *Shigella*, *Streptococcus, Proteus*, and *Enterococcus* were significantly increased in PD patients. Disease severity and PD duration negatively correlated with the relative abundance of cellulose degraders and positively correlated with the presence of putative pathobionts [61]. Sampson et al. reported that gut microbiota signature from PD patients showed a

decrease in *Prevotella, Lactobacillus, Peptostreptococcus,* and *Butyricicoccus* and an increase in *Proteus* and *Enterobacter* compared to healthy controls [56]. In contrast, another study reported that relative abundance of Prevotellaceae was significantly increased in PD patients. The relative abundance of Enterobacteriaceae was positively associated with the severity of postural instability and gait difficulty [62]. Minato et al. reported that a decrease of *Bacteroides fragilis* was found to be associated with worsening of motivation/initiative, and a decrease of *Bifidobacterium* was associated with worsening of hallucinations and delusions using the Unified PD Rating Scale over a period of 2 years [63]. Hasegawa et al. reported that relative abundance of *Clostridium coccoides* was increased in patients with early PD, while relative abundance of *Lactobacillus gasseri* was increased in patients with advanced PD [64]. Some studies have reported increased abundance of *Akkermansia* in PD patients [65–67]. *Akkermansia* degrades the mucus layer for energy source, and an increase of *Akkermansia* can result in the increased permeability of the intestinal mucus barrier.

24.3.2 How Does Gut Dysbiosis Affect the Development and Clinical Course of Parkinson's Disease?

To date, several mechanisms have been proposed on how gut dysbiosis can cause PD or exacerbate the symptoms of PD. First, the deficiency of SCFAs such as butyrate and propionate is observed with gut dysbiosis in PD patients [68–70]. Butyrate is an energy source for epithelial cells in colon [71], and its deficiency results in a reduced colonic motility and constipation [72]. Furthermore, the decrease of SCFA concentration can lead to an increase of intestinal permeability *via* chronic inflammation and a decreased expression of tight junction proteins including claudin 1 and claudin 2 [73, 74]. Also, SCFAs also contribute to the integrity of the blood brain barrier [75]. Intestinal dysbiosis leads to decreased claudin expression in the brain gut barrier. Also, the decrease of SCFA concentration leads to microglia dysfunction.

Second, gut dysbiosis with an increase of lipopolysaccharide (LPS)-producing bacteria can lead to the progression of PD. A decrease in serum LPS binding protein (LBP) levels is observed in PD [64, 66]. The increase of LPS concentration activates microglia and NLRP3 inflammasome and promotes the expression of iNOS [76, 77]. LPS induces progressive dopaminergic neurodegeneration in substantial nigra and decreased striatal dopamine levels [77–79].

Third, as mentioned above, the gut microbes can produce about half of all dopamine in human body. Gut dysbiosis alters the level of dopamine produced in the gut. Also, the concentration of SCFAs can affect the secretion of ghrelin, which decreases dopamine secretion in substantia nigra.

Fourth, bacterial amyloids can enhance progression of PD *via* inducing immune response to α-synuclein [80, 81].

24.3.3 Therapeutic Aspects of Gut Microbiota in Parkinson's Disease

Gut dysbiosis may precede glial cell dysfunction several years before the onset of PD [39]. Therefore, if gut dysbiosis can be normalized, the progression to PD can be prevented. SIBO is reported to be prevalent in PD patients with motor impairments. Since levodopa is absorbed from jejunum, SIBO may interfere with drug absorption through inflammation of the intestinal epithelium and/or altered levodopa metabolism by intraluminal bacteria [52]. Thus, antibiotics may improve motor fluctuations [52, 53]. In addition, some intestinal bacteria can metabolize levodopa, and it can be reversed by administering (S)-α-Fluoromethyltyrosine. As the bioavailability of the current levodopa/dopa decarboxylase inhibitor regimens appears to be very low, this could provide a new way to improve pharmacokinetics of the drug [82].

Probiotics may be beneficial in PD patients. Probiotics may reduce proinflammatory cytokines and enhance anti-inflammatory cytokines in PD patients [83], or reduce α-synuclein aggre-

gation [84]. Several studies have consistently shown that taking probiotics can improve constipation in PD patients [35, 85, 86]. Prebiotics can improve constipation and α-synuclein pathology, and reduced inflammation in PD patients [35, 70]. Recently, two pilot studies have suggested that fecal microbiota transplantation (FMT) may improve constipation and PD symptoms [87, 88]. There is a need to follow up the results of clinical studies on the effects of FMT on PD.

24.3.4 Can Gut Microbiota Changes Explain Sex Difference in Parkinson's Disease?

Sex differences in gut microbiota have been previously reported [89–91]. Also, sex-related differences in disease presentation and progression have been established in PD patients. Therefore, we can speculate that sex hormones affect the gut microbiota, leading to differences in the clinical manifestation of PD between men and women. The SCFA-producing bacteria such as *Prevotella*, *Ruminococcus*, and *Roseburia* are reported to depend on sex and hormonal status [92]. Serum estradiol level positively correlated with relative abundances of Gammaproteobacteria and Mixococcales, both Proteobacteria and LPS producers, and negatively correlated with relative abundance of Prevotellaceae, a SCFA producer in women [93, 94]. Estradiol-induced alterations in the gut microbiota may explain the increased risk of psychiatric disorders during puberty and reproductive age in women [92]. Since estrogen is thought to have a protective effect against PD, these findings may be inconsistent with the fact that PD is more prevalent in men than in women. However, since PD is a disease of the elderly and most women with PD are diagnosed after menopause, the effect of sex hormones on the clinical course of PD may be limited. The pathophysiology of PD may be more influenced by genetic and other environmental factors than gut microbiome.

Nonetheless, menopause or changes in sex hormones may affect the susceptibility to PD in women. Oral contraceptives and ovariectomy are also associated with changes in gut microbiota [95]. It has been reported that menopausal status might affect gut microbiota. That is, premenopausal women showed higher abundance of SCFA-producing bacteria than postmenopausal women and age-matched men [94, 96]. Young-onset PD (PD diagnosed <50 y) is known to be more prevalent in men [3]. Thus, these findings may provide one explanation on how sex differences can affect the susceptibility to PD *via* gut microbiota change. To date, there is sparse evidence on the changes in gut microbiome by sex in PD patients. In clinical studies involving changes in the gut microbiome of PD, both sexes are equally distributed within study groups, but the concept of sex differences is mostly underestimated or underreported. Therefore, further studies are necessary to clarify this issue.

24.4 Conclusions

Sex-related differences have been reported in PD. Several mechanisms have been proposed for sex differences in PD etiology. Recently, PD-specific gut microbiota signature has been reported, which may influence the pathogenesis or clinical course of PD. However, few studies have investigated the effect of gut microbiota on sex differences in PD. At present, we can only speculate the interactions between them. Gut microbiota may play a minor role in sex-related differences in PD. Nevertheless, this is a very interesting topic and further research is warranted in the future.

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The Impact of Oral Microbiome on Systemic Disease

25

Hyo-Jung Lee

25.1 Introduction

Surprisingly, few studies have meticulously investigated oral microbiome based on sex differences. It has long been estimated that nearly 700 different types of bacteria exist in the human oral cavity [1]. Currently, about 1000 species of the oral microbiome are known, and there is little interest in gender-based differences. Without accurate knowledge of gender differences in oral microbiome, analyses will lead to erroneous results. General information must be shared by clinicians in terms of oral microbime, Because the composition of oral microbiome is altered by therapeutic intervention. From a sex/gender perspective, a healthy oral microbiome will be revisited according to the stage of life such as pre-puberty and after puberty. The connection between the oral cavity and the body is the official slogan of the Forsyth Institute, which emphasizes the role of oral microbiome regarding oral disease progression followed by systemic diseases.

Recent studies have shown that the protective effect of estradiol is associated with estrogen receptor subtypes and specific tissue compartments associated with bacterial injury, suggesting that tissue-specific expression of specific sex steroid receptors increases the susceptibility to bacterial infection. Further, this gender bias depends on the effect of sex hormones on specific bacterial species [2]. This chapter is particularly helpful in understanding the link between oral and systemic diseases based on gender-based microbiome composition.

25.2 Dental Biofilm

The most diverse collections of oral microorganisms are found in dental plaque [3]. The biofilms that form on teeth are referred to as dental plaque [4]. It is now very common to use the term "dental biofilm" instead of the original descriptor "dental plaque." This does not mean that the original work performed on "dental plaque" is now invalid or irrelevant; rather it emphasizes the direct relevance of the broader principles based on studies of dental biofilms across the spectrum of microbiologic habitats.

The vast majority of microorganisms in nature, including those in the mouth, are attached to surfaces as biofilms. Biofilms have thus been defined as matrix-embedded microbial populations, adherent to each other and to surfaces or interfaces. It appears as a white or pale yellow "slime layer," that is commonly found between the teeth and along the gingival cervical margins

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(Fig. 25.1). Eventually, the biofilm changes from an early colony to a mature substrate [5] (Fig. 25.2). Whole oral cavity is covered by biofilm. Therefore, the composition of oral microbiome differs from the attached site in the oral cavity such as subgingival plaque supragingival plaque, keratinized gingiva, buccal mucosa, hard palate, tongue dorsum and saliva, tonsils, and throat [6].

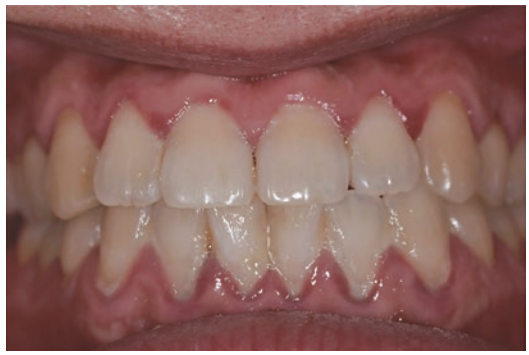

Fig. 25.1 Dental plaque (dental biofilm): Dental biofilms defined as matrix-embedded microbial populations, adherent to each other and to surfaces or interfaces

25.3 Sex-Based Differences in Healthy Oral Microbiome

In the absence of oral disease, the oral microbiome is influenced by genetic variation and environment. Recent studies support the role of contact and shared environment, and age (not genetics) as determinants of microbial transmission, consistently across species and strains and across multiple oral habitats [7]. However, this does not mean that heredity is not a factor in the composition of the oral microbiome. Host genetic factors, as well as environmental variables such as age, sex, and hormonal fluctuations, are also related to the human microbiome [8]. Oral bacteria change under major hormonal fluctuations, such as puberty or pregnancy, and hormonal changes may play a causal role in gender-specific microbial transitions [9]. The primary etiology of oral diseases is bacterial, and oral bacterial profiles vary by sex. The effect of sex steroids on subgingival bacteria is obvious by the cumulative impact of puberty, menstruation, oral contraceptives, and pregnancy on long-term changes in the

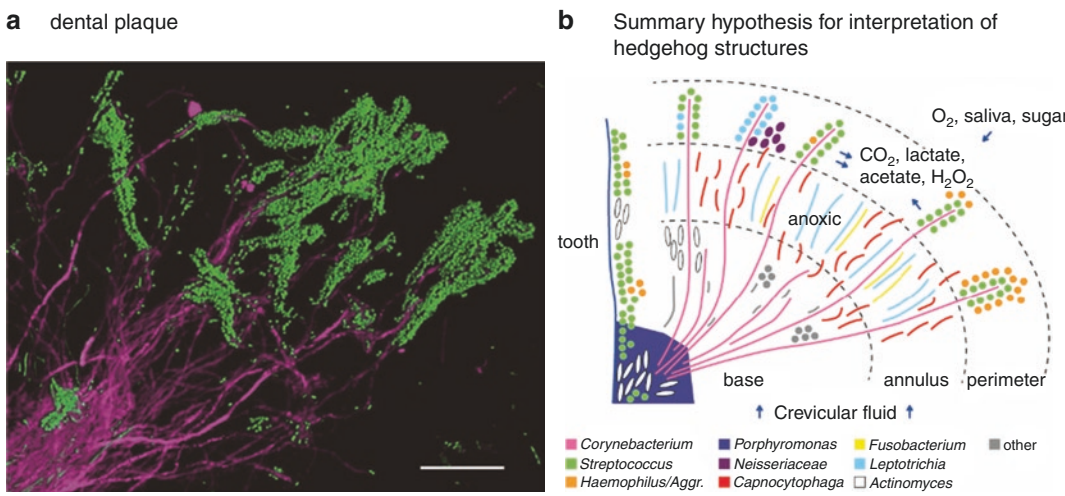

Fig. 25.2 (**a**) Dental plaque: Corncob structures formed by *Corynebacterium* and cocci in plaque. *Corynebacterium* cells (magenta) are visible as long filaments, with cocci (green) bound to the tips of the filaments (Scale bar: 20 μm). (**b**) Summary hypothesis for the interpretation of hedgehog structures: The base of the hedgehog is dominated by *Corynebacterium* filaments and thinly populated by additional rods, filaments, and cocci (adapted from Welch et al. [5])

female subgingival microbiome reported by studies investigating the association between sex and the composition of oral microbiome in health and disease [10].

The role of oral microbiome in childhood is not clearly established. Children aged 2–12 years carry high levels of *Actinomycetes*, some of which increase the risk of caries, indicating that these microbes may not be a major determinant influencing dental caries in girls without caries [11].

Basically, the biochemical parameters of saliva differ according to gender. Salivary pH, buffering capacity, protein content, secretion-IgA, and chitinase activity were all lower in females than in males, whereas lysozymal activity was higher [12]. Zaura et al. reported gender-specific differences in microbiome and metabolites. Samples with high salivary pH showed increased chitinase activity, higher abundance of *Veillonella* and *Prevotella* species, and higher levels of amino acid fermentation products, suggesting proteolytic adaptation. Linear discriminant analysis effect size (LEfSe) revealed 65 unique OTUs between males and females, of which 44 OTUs (including 19 streptococcal OTUs) were significantly higher in females, whereas the male salivary microbiome was higher in *Veillonella*, *Prevotella*, and *Megasphaera*. The results also suggested that overspecialization of proteolytic or saccharolytic ecotypes may indicate a transition to a dysbiotic state (Fig. 25.3). Low salivary pH in female is attributed to physiological factors such as the effect of sex hormones on salivary gland gene expression and smaller salivary gland size [13]. The oral cavity harbors a high degree of bacterial diversity [3]. It is also known to carry a very diverse viral community [14]. Many of these oral viruses are not transient members of the oral ecosystem, as evidenced by persistence of specific viruses over the entire 60-day study period. In

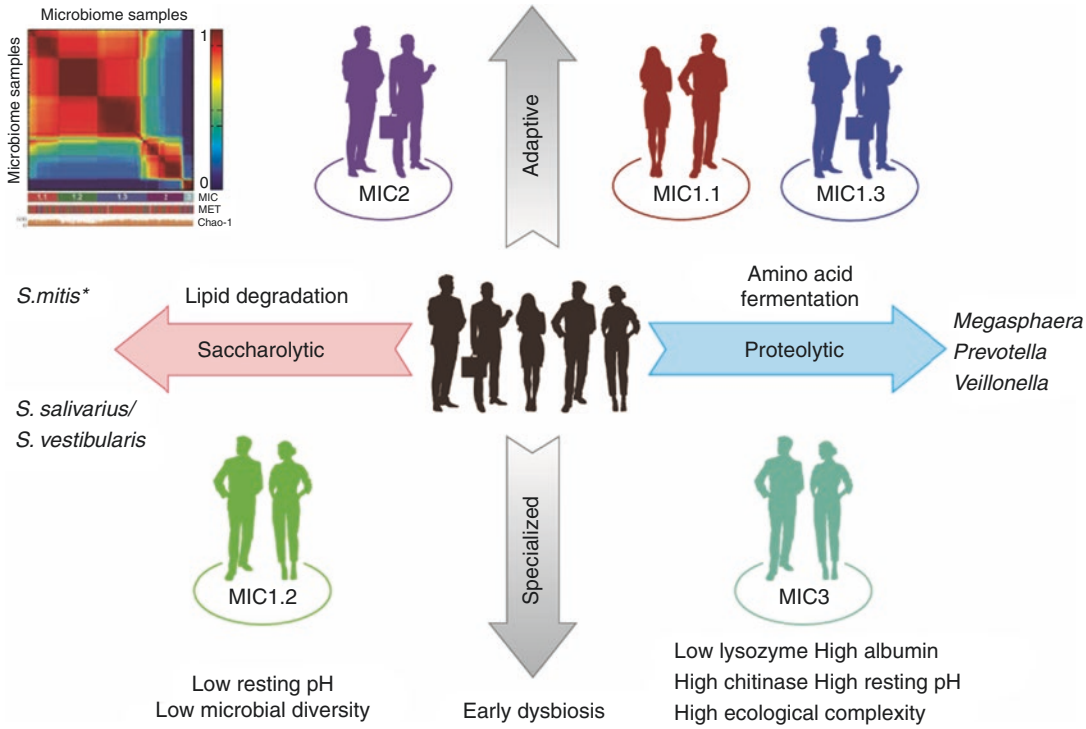

Fig. 25.3 Salivary ecosystem in healthy young adults: The dichotomy in bacteria-metabolite associations and the relation with salivary parameters is depicted in saccharolytic (left side) and proteolytic (right side) adaptations of the ecosystem. MIC 1.2.3: Clusters of three main microbiome samples (adapted from Zaura et al. [12])

this study, differences between viromes were attributed to sex differences of the host rather than differences between individuals.

25.4 Oral Microbiome and Oral Disease Based on Sex

Salivary microbiome studies investigating oral disease status report differences between healthy and dysbiotic microbiomes, such as dental caries or periodontal diseases [15, 16].

In general, men are more susceptible to periodontal disease [17]. Women have significantly higher saliva pH than men, but women are more susceptible to dental caries due to multiple reasons such as biological and anthropological factors [18].

25.4.1 Oral Microbiome in Dental Caries by Sex

Streptococcus mutans and *Lactobacillus* are classically cariogenic microbial species [19]. Additional microorganisms that are associated with caries include *Scardovia wiggsiae, Firmicutes, Veillonella* HOT 780*, Slackia exigua, Porphyromonas, Granulicatella elegans, and Actinomyces* [20]. These cariogenic bacteria produce an acidic environment by breaking down fermentable carbohydrates, suggesting that diet and specific nutrients are key determinants of dental caries. In 2019, Ortiz et al. reported significant sex differences in salivary microbiota between caries-active boys and girls. *Neisseria flavescens, Rothia aeria, and Haemophilus pittmaniae* were found at significantly higher levels in caries-active boys [11]. In contrast, *Lactococcus lactis, Selenomonas* species HOT 126, *Actinobaculum* species HOT 183, *V. parvula, and Alloprevotella* species HOT 473 were found at significantly higher levels in caries-active girls aged 2–12 years (Fig. 25.4). Thus, the levels of acid-producing caries-inducing *L. lactis* were significantly higher in caries-active girls than in caries-active boys. In addition, in caries-active girls, *Alloprevotella* species HOT 473 was the only species that exhibited significant sex differences (4.4-fold difference; $p = 0.0003$) and increased abundance (1.85% of the total micro-

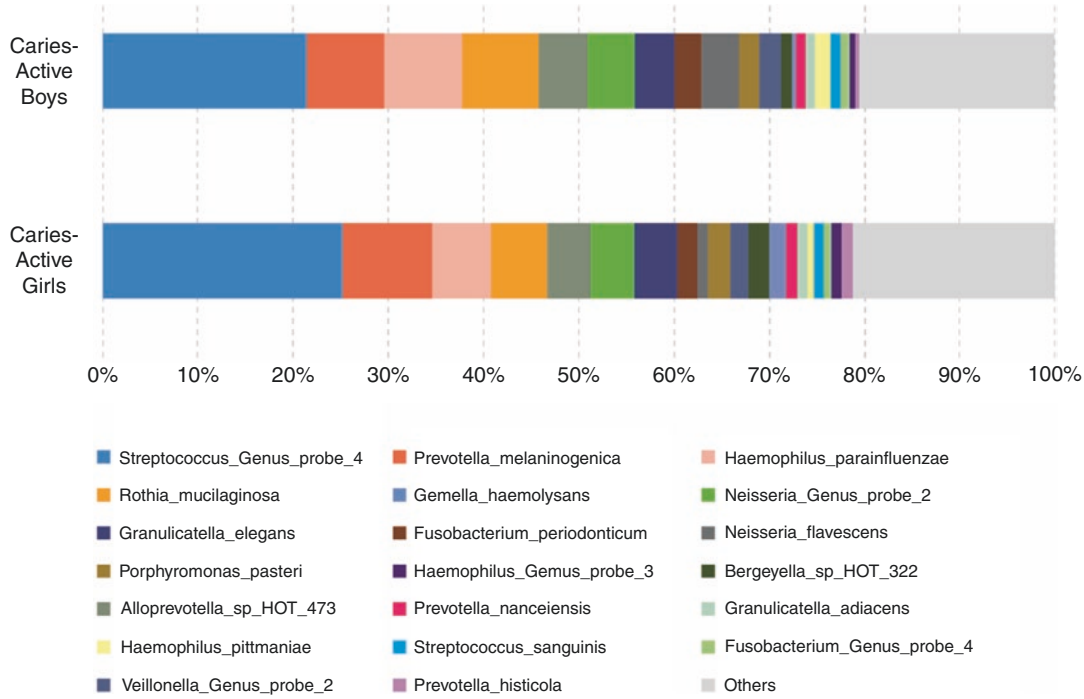

Fig. 25.4 Abundance of top 20 salivary microorganisms found in caries-active and caries-free children differentiated by sex (adapted from Ortiza et al. [11])

bial population). Other early caries studies reported significant differences in the abundance of *Neisseria* between males and females diagnosed with severe childhood caries [21]. Due to multiple risks, including cultural issues, female gender is more susceptible to caries than men in remote areas [22]. However, the diminished flow rate of saliva contributes to a less protective oral environment and greater caries susceptibility. The parotid, buccal, and lip salivary glands showed lower flow rates in females than in males, especially among elderly participants [23]. Smaller salivary glands in women consistently showed substantially lower IgA concentrations among all salivary glands tested, and the higher IgA concentrations in men may be associated with a greater protection against caries when compared with women [24].

25.4.2 Oral Microbiome in Periodontal Disease by Sex

The incidence and severity of periodontal disease were higher in men [25]. Umeda et al. reported that men have greater odds of carrying *P. intermedia* in saliva, subgingival and supragingival plaques [8]. Periodontal disease during a hormone surge suggests that inflammation occurs due to the hormonal effect on the gingival tissue and the subgingival ecosystem. Since these hormonal variations are systemic, it may be useful to investigate whether host-associated bacterial ecosystems elsewhere in the body respond similar to that of subgingival bacteria [9]. Moore et al. reported increased levels of *Lactobacillus rimae* (now *Atopobium rimae*), *P. denticola*, *Actinomyces naeslundii*, and *V. atypica* in pubertal boys [26]. Immediately after the onset of puberty, *P. intermedia* and *P. melaninogenica* were detected mostly in boys, whereas *Actinomyces odontolyticus* was more frequently detected in girls [27]. Within the oral environment, *Prevotella* spp. (*P. intermedia* and *P. nigrescens*) were found in both healthy periodontal furrows and diseased periodontal pocket, but their frequency and rate of detection in healthy individuals was significantly lower than in disease [28].

Prevotella species also secrete potent lipopolysaccharides that stimulate osteoclast formation and nitric oxide release from macrophages in vitro [29]. Exopolysaccharide is another recently identified virulence factor that appears to confer resistance to phagocytosis by polymorphonuclear leukocytes [30, 31].

25.5 Oral Microbiome and Systemic Diseases

Previous studies have reported that the salivary microbiome is more resilient and stable despite changes in diet and oral hygiene compared with the gut microbiota. The oral microbiome contains a wealth of information including not only the oral health, but also the systemic health of the whole body.

25.5.1 Oral Microbiome and Metabolic Diseases by Sex

Raju et al. determined the association between salivary microbiota and body size in Finnish children aged 11–14 years based on gender [32]. Oral microbiome in boys was more alpha-diverse than girls. The composition differed between normal-weight and obese girls, but not in boys. The levels of *Veilonella, Prevotella, Selenomonas*, and *Streptococci* were reduced in obese children. Among young adults in their 20s, differences could be observed in saliva microbiota between men and women in the fasted condition but even more in the fed condition, and *Porphyromonas* and *Capnocytophaga* were overrepresented in the male salivary samples compared with female saliva [33]. This study suggests that gender was associated with a particular "signature" of oral microbiota in fed and fasted conditions. Therefore, the sex-related differences after feeding require further characterization as part of a generalized concept of "personalized medicine." Bacterial signatures of belonging to the male gender were identified under fed conditions: Lentimicrobiaceae and *Capnocytophaga* were

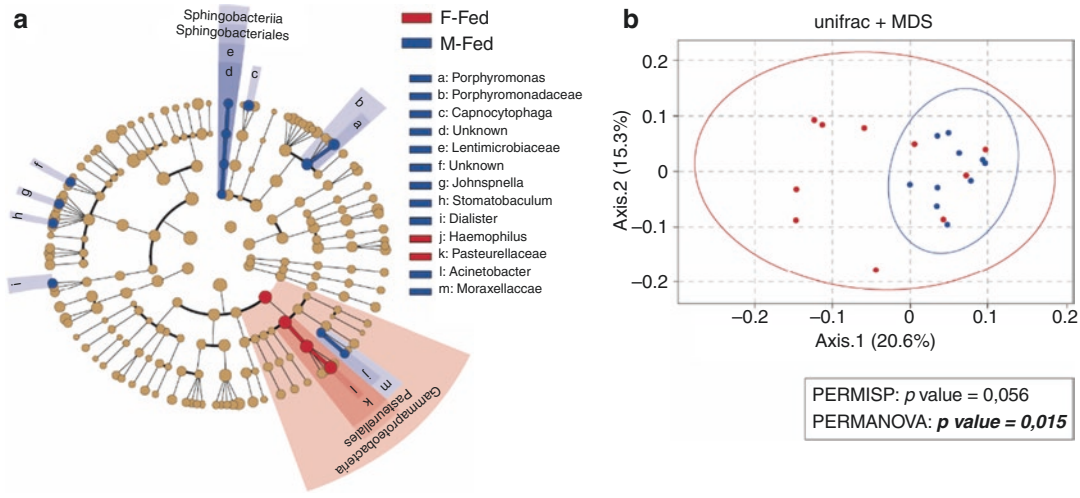

Fig. 25.5 (**a**) Oral (saliva) microbiota in fed condition in female subjects compared with male subjects: Linear discriminant analysis effect size (LEfSe) analysis-based cladogram. (**b**) Unifrac representation of the beta diversity between fed female and fed male (adapted from Minty et al. [33])

overrepresented in the male salivary samples and partly contributed to the "male microbiota" signature.

Similarly, the genus *Haemophilus* from the family Pasteurellaceae was overrepresented in the female salivary samples after feeding and represented the signature of female salivary microbiota [33] (Fig. 25.5).

25.5.2 Oral Microbiome and Gastrointestinal Diseases by Sex

Recent studies suggest that the oral microbiome plays a role in the health of other extremities in the body. For example, the enrichment of both *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in oral cavity has been associated with a higher risk of pancreatic cancer [34]. The relative abundance of *Streptococcus* and *Prevotella* species was higher in the oral cavity of individuals with colorectal cancer [35]. However, it is still unknown whether oral inflammation in patients with gastrointestinal (GI) diseases is the cause or a consequence of imbalance in the salivary microbiota, and which local (oral cavity) or systemic (gut) immune response is responsible for the apparent dysbiosis of salivary microbiota. Further studies are needed to elucidate the sex-dependent oral microbiome in patients with GI diseases.

25.5.3 Oral Microbiome and Cardiovascular Diseases by Sex

Kwun et al. investigated the microbial diversity and composition of coronary thrombus in patients with ST-segment elevation myocardinal infarction (STEMI), and the composition of thrombus microbiome compared with oral and intestinal microbiota [36]. The patient group presented microbial dysbiosis characterized by a higher relative abundance of *Proteobacteria* (p) and *Enterobacteriaceae* (f) in the gut microbiome and a lower abundance of *Firmicutes* (p) and *Haemophilus* (g) in the oral microbiome. Currently, most studies related to oral microbiome in patients diagnosed with cardiovascular diseases are focused on male gender.

25.6 Conclusions

The salivary microflora exhibits temporal stability, with little or no evidence of diurnal activity compared with stool [37]. Fluctuations indicate that saliva sampling time is not a critical parameter [37]. The composition of the oral microbiome is influenced by several factors, including gender. A well-designed study investigating the role of gender in oral disease is needed.

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Part XI

Overlap Syndrome of Functional Gastrointestinal Disorders

Overlap Syndrome of Functional Gastrointestinal Disorders

26

Nayoung Kim

26.1 Introduction

The Rome Foundation, a committee of experts, published the Rome Criteria IV in 2016 and categorized functional gastrointestinal disorders (FGIDs) in the digestive organs into esophageal, gastroduodenal, bowel, gastrointestinal (GI) pain, gallbladder and sphincter of Oddi, anorectal disease, neonate/toddler, and child/adolescent diseases [1] (Table 26.1). GI motility disorder, visceral hypersensitivity, infection, inflammation, and changes in the gut microbiota are hypothesized to be important pathophysiological mechanisms. In recent years, as studies have explored interactions within the brain-gut-microbiome axis, the biopsychosocial model has become prominent as a way to explain GI symptoms as a result of paresthesia, changes in motility, the combined activation of the autonomic and central nervous systems, and interactions involving the gut microbiota. Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most common FGIDs. Depending on the definition used and the population in each study, the prevalence of IBS was 3–27% and that of FD was 25% [2]. These two diseases have a shared pathophysiology; this increases the probability of these diseases occurring together, which is referred to as overlap syndrome of FGID, about which numerous studies have been published [3–12].

A notable characteristic of overlap syndrome of FGID is that, in addition to GI symptoms, patients with overlap syndrome report physical and psychological symptoms, such as fibromyalgia, migraine, joint pain, temporomandibular joint disorder, bladder pain syndrome, interstitial cystitis, anxiety, and depression, and they are more likely to be female and have accompanying pain [13]. Therefore, rather than simply approaching overlap syndrome as a combination of IBS and FD, there is a need for research focusing specifically on overlap syndrome of FGID as a condition that is more severe and is more frequent in women, for which reason it is important to understand sex/gender differences in this disease. In this chapter, the definition, distribution, and pathophysiology of overlapping syndrome of FGID are explored.

26.2 Distribution of Overlap Syndrome of Functional Gastrointestinal Disorders

The Rome Foundation defines each FGID separately [1] (Table 26.1), but in clinical practice, it is common to observe two or more FGIDs at the same time. Population-based epidemiological studies have similarly reported overlapping syn-

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Table 26.1 Categorization of FGIDs in the Rome IV criteria (adapted from Drossman and Hasler [1])

A. Esophageal disorders	
A1. Functional chest pain	A4. Globus
A2. Functional heartburn	A5. Functional dysphagia
A3. Reflux hypersensitivity	
B. Gastroduodenal disorders	
B1. Functional dyspepsia	B3. Nausea and vomiting disorders
B1a. Postprandial distress syndrome (PDS)	B3a. Chronic nausea vomiting syndrome (CNVS)
B1b. Epigastric pain syndrome (EPS)	B3b. Cyclic vomiting syndrome (CVS)
B2. Belching disorders	B3c. Cannabinoid hyperemesis syndrome (CHS)
B2a. Excessive supragastric belching	B4. Rumination syndrome
B2b. Excessive gastric belching	
C. Bowel disorders	
C1. Irritable bowel syndrome (IBS)	C2. Functional constipation
IBS with predominant constipation (IBS-C)	C3. Functional diarrhea
IBS with predominant diarrhea (IBS-D)	C4. Functional abdominal bloating/distension
IBS with mixed bowel habits (IBS-M)	C5. Unspecified functional bowel disorder
IBS unclassified (IBS-U)	C6. Opioid-induced constipation
D. Centrally mediated disorders of gastrointestinal pain	
D1. Centrally mediated abdominal pain syndrome (CAPS)	
D2. Narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia	
E. Gallbladder and sphincter of Oddi (SO) disorders	
E1. Biliary pain	E2. Functional pancreatic SO disorder
E1a. Functional gallbladder disorder	
E1b. Functional biliary SO disorder	
F. Anorectal disorder	
F1. Fecal incontinence	F3. Functional defecation disorders
F2. Functional anorectal pain	F3a. Inadequate defecatory propulsion
F2a. Levator ani syndrome	F3b. Dyssynergic defecation
F2b. Unspecified functional anorectal pain	
F2c. Proctalgia fugax	
G. Childhood functional GI disorders: neonate/toddler	
G1. Infant regurgitation	G5. Functional diarrhea
G2. Rumination syndrome	G6. Infant dyschezia
G3. Cyclic vomiting syndrome (CVS)	G7. Functional constipation
G4. Infant colic	
H. Childhood functional GI disorders: child/adolescent	
H1. Functional nausea and vomiting	H2a2. Epigastric pain syndrome
H1a. Cyclic vomiting Syndrome (CVS)	H2b. Irritable bowel syndrome (IBS)
H1b. Functional nausea and functional vomiting	H2c. Abdominal migraine
H1b1. Functional nausea	H2d. Functional abdominal pain – NOS
H1b2. Functional vomiting	H3. Functional defecation disorders
H1c. Rumination syndrome	H3a. Functional constipation
H1d. Aerophagia	H3b. Nonretentive fecal incontinence
H2. Functional abdominal pain disorders	
H2a. Functional dyspepsia	
H2a1. Postprandial distress syndrome	

drome, wherein various FGIDs co-occur [7–9, 14–16] (Table 26.2). For example, the prevalence of IBS among patients with FD is 37%, which is substantially higher than the prevalence of 7% among those who do not have FD. The odds ratio (OR) of IBS in patients with FD is high, at 8 (95% confidence interval [CI], 5.74–11.16) [17]. The prevalence of FD when IBS is present is

Table 26.2 Trends of overlap syndrome in primary clinics and tertiary hospitals (adapted from Park et al. [8])

	Primary clinics (n = 155)	Tertiary hospitals (n = 236)	Total (N = 391)
Combined FGIDs	84 (54.2%)	117 (49.6%)	201 (51.4%)
FD + IBS	35 (22.6%)	53 (22.5%)	88 (22.5%)
FD + belching disorders	25 (16.1%)	45 (19.1%)	70 (17.9%)
IBS + belching disorders	20 (12.9%)	30 (12.7%)	50 (12.8%)
FD + functional heartburn	16 (10.3%)	24 (10.2%)	40 (10.2%)
IBS + functional heartburn	5 (3.2%)	15 (6.4%)	20 (5.1%)
Functional heartburn + belching disorders	10 (6.5%)	19 (8.1%)	29 (7.4%)
FD + IBS + belching disorders	14 (9.0%)	24 (10.2%)	38 (9.7%)
FD + IBS + functional heartburn	5 (3.2%)	14 (5.9%)	19 (4.9%)
FD + belching disorders + functional heartburn	8 (5.2%)	13 (5.5%)	21 (5.4%)
IBS + belching disorders + functional heartburn	4 (2.6%)	9 (3.8%)	13 (3.3%)
FD + IBS + belching disorders + functional heartburn	4 (2.6%)	9 (3.8%)	13 (3.3%)

FGIDs functional gastrointestinal disorders, *FD* functional dyspepsia, *IBS* irritable bowel syndrome

29–87% [16, 18, 19]. These high prevalence rates imply the possibility that shared components of pathophysiology such as GI motility disorder, visceral hypersensitivity, infection, inflammation, and changes in the gut microbiota are expressed in both the stomach and intestines, rather than overlap by chance. Support for this possibility is provided by the ongoing publication of reports about FGIDs other than IBS and FD [2]. In an age-representative survey about 20 types of FGIDs conducted in the United States, 69% of respondents had at least one FGIDs [20], and in a population-based survey, 1–8% of the general population had multiple FGIDs [16]. A study of the general population in Olmsted County, Minnesota in the United States also reported that 17% of individuals had two or more FGIDs, including symptoms of gastroesophageal reflux disease (GERD) [21]. Among reports from Asia, a cross-sectional study of individuals participating in health check-ups in Japan found that the prevalence of FD was 10.0%, that of IBS was 14.2%, and that of overlap syndrome of FD and IBS was 3.4% [5]. In a South Korean study of individuals participating in health check-ups and inpatients, 15.0% had overlap syndrome of FD and IBS, and patients with overlap syndrome reported more symptoms of depression and lower quality of life (QoL) than individuals with no FGIDs [4]. A study conducted among patients visiting gastroenterology clinics in China reported overlap syndrome of IBS and FD in 5% of the samples [3]. The prevalence of overlap syndrome of FD and IBS reported in Asia ranges from 11.4% [9] to 27.6% [4] (Table 26.3) [7]; this discrepancy might reflect variation across different cohorts or study designs. When more severe FGIDs are included, the proportion of overlap syndrome increases, but when multiple less severe symptoms are included, the proportion is expected to decline. In a study by the author's research team conducted among gastroenterology outpatients, the proportion of patients with overlap syndrome of FD and IBS was high, at 31.0% [11]. When the subtypes of FD and IBS were compared, overlap of postprandial distress

Table 26.3 Overlap syndrome of functional dyspepsia and irritable bowel syndrome in Asia (modified from Suzuki and Hibi [7])

	FD alone (n [%])	IBS alone (n [%])	FD-IBS overlap (n [%])
Wang et al. [3]	306 (48.2)	178 (28.0)	151 (23.8)
Nakajima et al. [6]	17 (34.0)	21 (42.0)	12 (24.0)
Kaji et al. [5]	177 (31.7)	289 (51.8)	92 (16.5)
Lee et al. [4]	28 (18.4)	82 (53.9)	42 (27.6)
Park [9]	72 (43.1)	76 (45.5)	19 (11.4)
Choi et al. [11]	198 (56.0)	46 (13.0)	110 (31.0)

FD functional dyspepsia, *IBS* irritable bowel syndrome

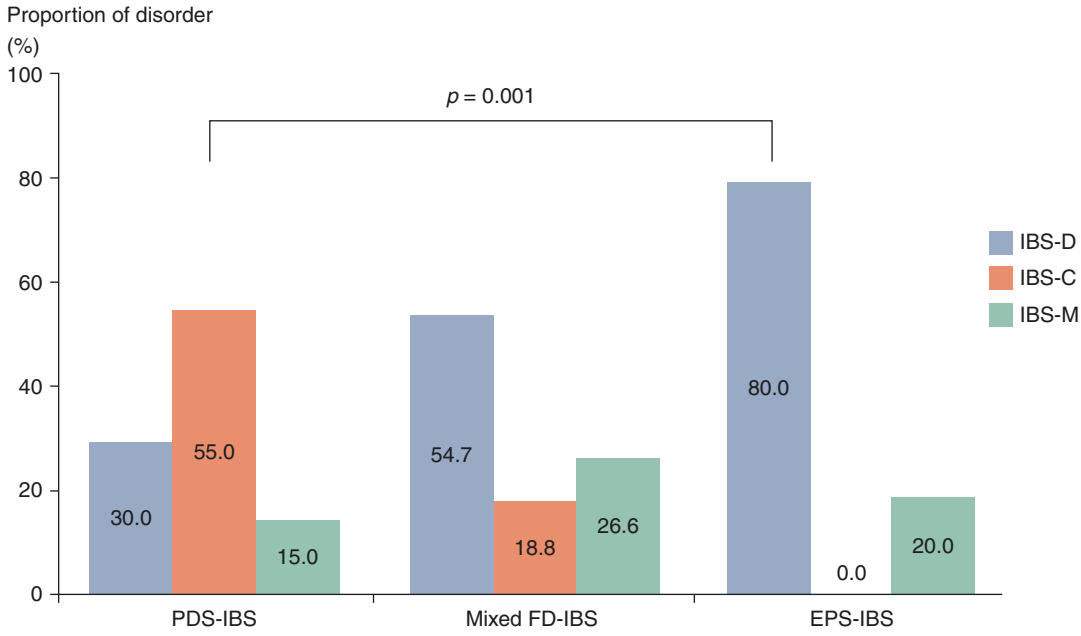

Fig. 26.1 The distribution of subtypes of irritable bowel syndrome by subtypes of functional dyspepsia. Overlap with irritable bowel syndrome with predominant constipation was common in the PDS subtype of functional dyspepsia, while irritable bowel syndrome with predominant diarrhea was frequently observed in the EPS subtype of functional dyspepsia. *PDS* postprandial distress syndrome, *EPS* epigastric pain syndrome (adapted from Choi et al. [11])

syndrome (PDS)-subtype FD with IBS with predominant constipation (IBS-C) was the most common [11] (Fig. 26.1). FD of the epigastric pain syndrome (EPS) subtype, where pain is experienced regardless of food consumption, and IBS with predominant diarrhea (IBS-D) also commonly overlapped [11] (Fig. 26.1). The former combination was much more common in women than in men [11].

26.3 Symptoms of and Sex/Gender Differences in Overlap Syndrome

In a study conducted by the author's research team with 354 patients who had either FD or IBS diagnosed using the Rome III criteria and 278 controls, the patients with overlap syndrome were younger than those with only FD (47.2 ± 13.8 vs. 51.9 ± 2.9 years, $p = 0.003$) and were more likely to be women (66.4% vs. 45.7%, $p = 0.016$) [11]. Compared to those with either FD or IBS, patients with overlap syndrome of FGID were more likely to be single, divorced, or widowed (30.9% vs. 13.1%, 30.9% vs. 13.0%, respectively, both $p < 0.05$). The depression score and the proportion of those who drank ≥70 g of alcohol per week were higher among patients with overlap syndrome than among those with FD only (depression score: 10.1 ± 3.5 vs. 7.3 ± 3.3, $p = 0.028$; alcohol: 26.9% vs. 7.1%, $p = 0.01$). However, the proportion of smokers was lower among patients with overlap syndrome than in other disorder groups [11]. Nausea, abdominal bloating, and a feeling of incomplete emptying after bowel movements were independent risk factors for overlap syndrome compared to separate disorders. Young age, depression score, abdominal bloating, and PDS were independent risk factors for overlap syndrome compared to FD [11]. Symptom severity was higher and QoL was much lower in patients with overlap syndrome than in patients with either FD or IBS [11] (Fig. 26.2). In another Korean multicenter study (334 healthy controls, 168 with FD-only,

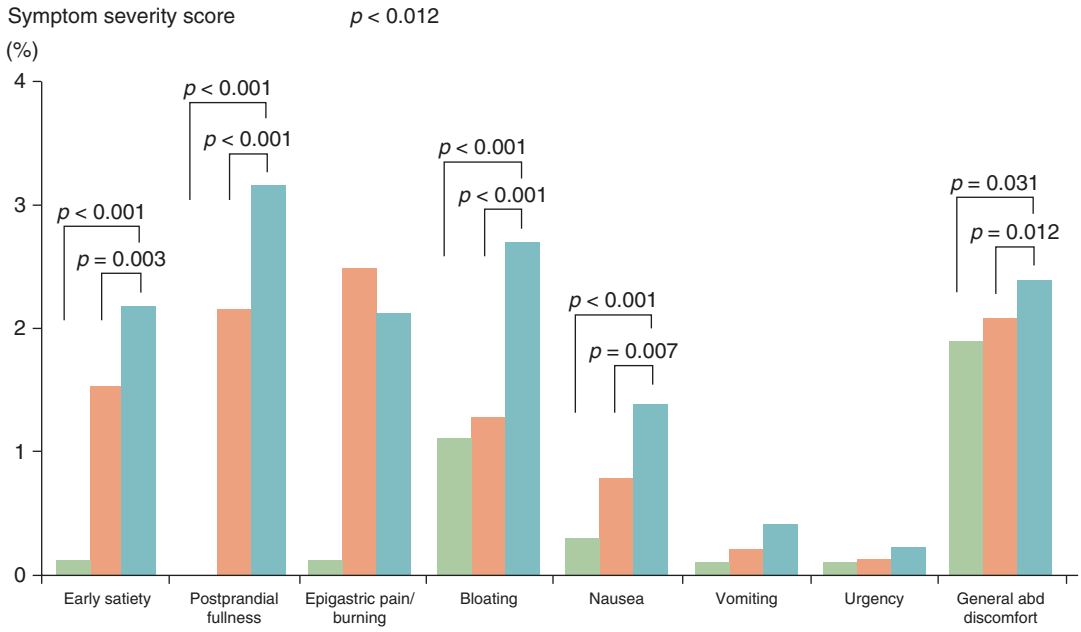

Fig. 26.2 Comparison of the severity of digestive symptoms among irritable bowel syndrome only, functional dyspepsia only, and overlapping syndrome (adapted from Choi et al. [11])

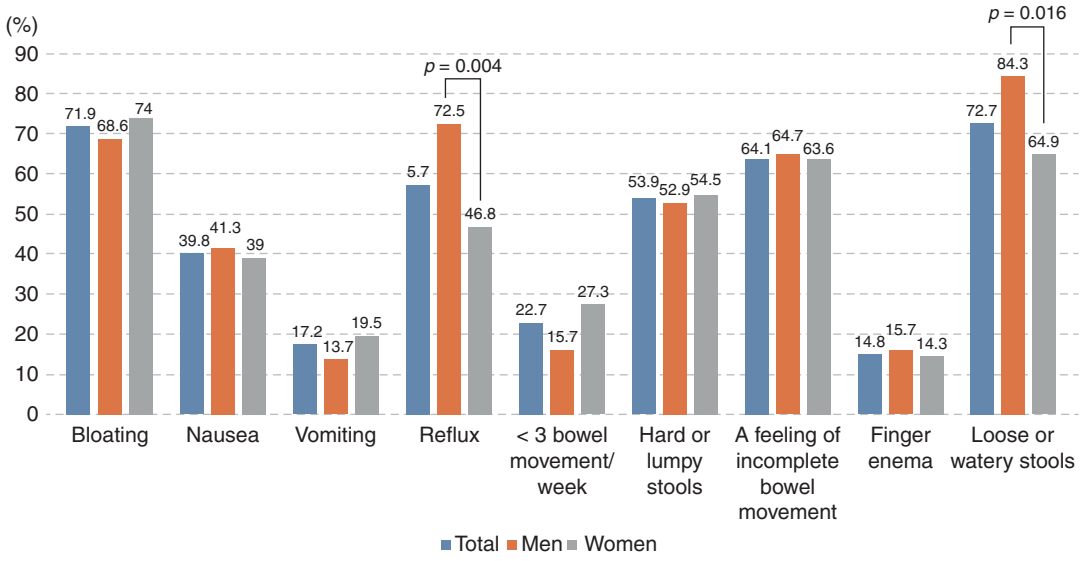

Fig. 26.3 Gender difference in the frequency of representative gastrointestinal symptoms in patients with overlap syndrome of functional dyspepsia and irritable bowel syndrome (adapted from Nam et al. [22])

37 with IBS-only, 128 with FD-IBS overlap), the overlap group (19.2%) showed a higher rate of preference for dairy products, higher rate of history of *Helicobacter pylori* eradication, and higher anxiety/depression scores than the non-overlap group ($p < 0.05$). In the FD-IBS overlap group, men complained of reflux symptom and loose/watery stools more than women ($p < 0.05$), whereas women showed more severe GI symptoms, especially epigastric pain/burning symptoms, and higher depression scores than men (all $p < 0.05$) [22] (Fig. 26.3).

Overlap syndrome of FGIDs is more common among women than men. Women with overlap syndrome of FGIDs are more likely to have female-specific diseases such as dysmenorrhea, endometriosis, adenomyosis, leiomyomas, pelvic floor myalgia, vulvodynia, chronic cyclic pelvic pain, dyspareunia, and polycystic ovary syndrome than women without GI disorders. Hysterectomy was three-times more prevalent among patients who had IBS than among those who did not [13, 23] and was significantly more prevalent among patients with overlap syndrome of FGIDs [11], suggesting that when gynecological diseases co-occur with IBS, the possibility of healthcare-seeking is high, which leads to surgical interventions [13]. The reasons why gynecological diseases are common among patients with FGIDs, especially IBS, are related with brain activation patterns, dysregulation of the hypothalamic-pituitary-adrenal axis, immune dysfunction, visceral and somatic pain sensitivity alterations, autonomic nervous system dysregulation, and genetic susceptibility [13]. As the cause and pathophysiology of each symptom of FGIDs are complex and multifactorial, it is difficult to pinpoint a single main cause, which can vary from person to person [13]. The gender difference that women visit healthcare institutions more frequently may also be a relevant causal factor, although this phenomenon varies across countries.

26.4 Pathophysiology of Overlap Syndrome

A persuasive explanation for overlap syndrome is that two or more diseases that share the same pathophysiology (e.g., visceral hypersensitivity and GI motility disorder) can occur in multiple organs, instead of being limited to one organ. For example, abnormalities in GI smooth muscles can be a common cause of GERD, FD, and IBS-C [24, 25]. Resting-state lower esophageal sphincter pressure measured with esophageal manometry was significantly lower in patients with IBS than in those without IBS [26], and visceral hypersensitivity—as an important component of the pathophysiology of FGIDs—has been proposed as a common mechanism of various FGIDs, including GERD [27–29]. For example, the threshold for pain recognition in the rectum was found to be lower in patients with IBS, and similarly, the threshold for recognition and discomfort sensation in the esophagus was significantly lower [30]. Patients with FD also had a significantly lower threshold for recognition and discomfort sensation in the esophagus and for pain recognition in the rectum than their counterparts [30]. The pathophysiology of FD, such as a delay in gastric emptying time and visceral hypersensitivity, has been suggested as the mechanism for 10–40% of cases of GERD that is nonresponsive to proton pump inhibitors [31, 32], which are effective medications for treating GERD [24, 31]. This indicates that some patients with GERD, especially those with overlap syndrome, have a disease similar to FGIDs rather than gastric acid reflux [2]. When overlap syndrome includes GERD, visceral hypersensitivity is not limited to a specific GI area and it was supported by our study [33]. We included nonerosive reflux disease or reflux hypersensitivity in addition to FD, and IBS in the analysis of FGID overlap syndrome (Fig. 26.4a) and we found sex/gender differences in FGID, especially in the overlap group [33] (Fig. 26.4b). That is, non-erosive reflux disease (NERD)/reflux hypersensitivity (RH) was significantly more prevalent in men and FD was more prevalent in women [33] (Fig. 26.4b). Overlap FGIDs were more prevalent than non-overlap FGIDs in women. Anxiety and depression scores were higher in the overlap FGIDs, and FGID symptoms (early satiation, postprandial fullness, and epigastric pain) were more frequent and severe in the overlap FGIDs than in the non-overlap groups [33]. Our study supports that FGIDs alternatively or concurrently occur throughout the entire stomach and intestines [34]. Overlap between the PDS subtype of FD and IBS-C is especially common (Fig. 26.1), and its suggested pathophysiology is not limited to visceral hypersensitivity, but also includes infection, immune function abnormalities, gut microbiota abnormalities, dysmotility, psychological factors, altered brain activation,

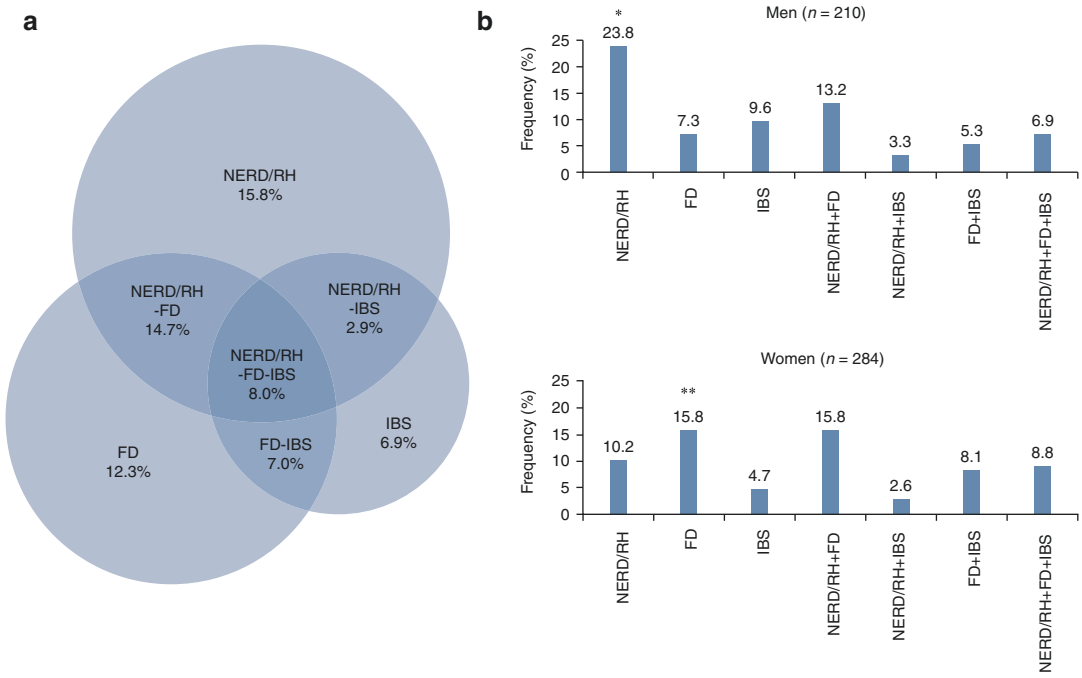

Fig. 26.4 Proportions of subjects with FGIDs (**a**) and distribution of FGIDs according to sex (**b**). The prevalence of NERD was significantly higher in men and that of FD was significantly higher in women. *$p < 0.0001$ compared with women NERD, **$p < 0.0001$ compared with men FD. *FGID* functional gastrointestinal disorder ($n = 494$), *NERD* non-erosive reflux disease or *RH* reflux hypersensitivity ($n = 304$), FD functional dyspepsia ($n = 308$), *IBS* irritable bowel syndrome ($n = 180$), non-overlap FGIDs ($n = 255$), overlap FGIDs ($n = 239$) (adapted from Lee et al. [33])

and genetic factors [11]. In addition to GI symptoms, patients with overlap syndrome of FGIDs tend to have physical and psychological symptoms such as fibromyalgia, migraine, joint pain, temporomandibular joint disorder, bladder pain syndrome, interstitial cystitis, anxiety, and depression, as well as pain [13] (Fig. 26.5).

26.5 Course and Overlap Syndrome of Functional Gastrointestinal Disorders

Generally, GI symptoms fluctuate between improvement and deterioration with time. According to a short-term follow-up study of FGIDs in the Swedish general population by Bolling-Sternevald et al., around 72–81% reported the same symptoms around 3 months after reporting symptoms of GERD, FD, or IBS [35]. This result indicates that there are not very many short-term changes in FGIDs, and most symptoms do not change. However, in a population-based study that observed changes in FGIDs with a longer follow-up, unlike the findings from the previous study, changes in other FGIDs were observed in many cases [2]. According to a study about 1-year and 7-year changes in FGIDs, including GERD, conducted in Sweden by Agréus et al., the prevalence of FGIDs, including GERD, was similar, and more than 50% of those who had symptoms of IBS in the first survey had the same symptoms 1 year and 7 years after [14]. However, many cases became asymptomatic or had different symptoms [14]. In a study conducted by Halder et al. that followed up FGIDs for 12 years, only around 20% of patients who were identified as patients with FGIDs in the earlier surveys had the same FGIDs 12 years later, 40% became asymptomatic, and 40% had different FGIDs [36]. This finding indicates that FGIDs remain the same in

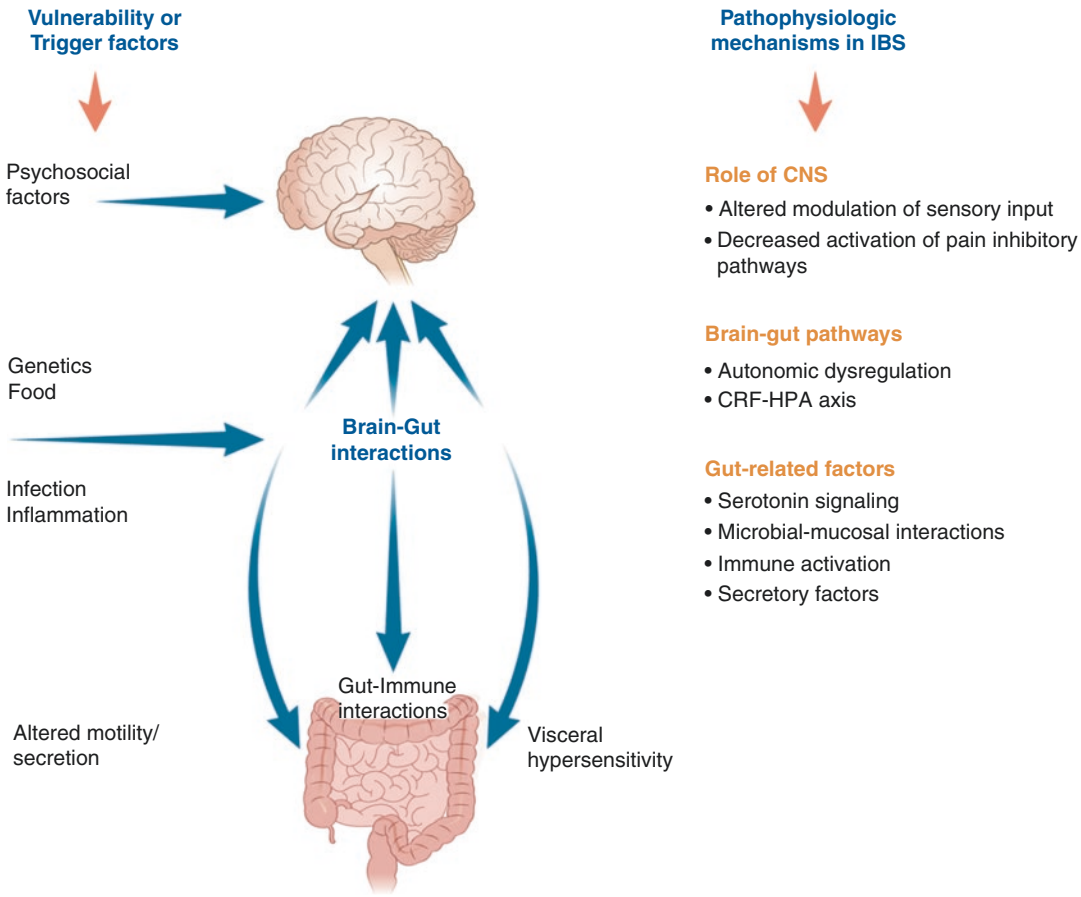

Fig. 26.5 Model of factors that cause psychiatric symptoms with irritable bowel syndrome. *CNS* central nervous system, *CRF-HPA axis* corticosteroid releasing factor-hypothalamus pituitary adrenal (adapted from Chang and Drossman [15])

some patients, become different FGIDs in others, and resolve in a substantial proportion (40%) [2, 36]. Similarly, Aro et al. conducted a study that followed up FGIDs for 10 years [34]. Although the symptoms started as FD, GERD, and IBS, during the 10-year follow-up, they evolved into other FGIDs, and in this process, overlap syndrome was commonly observed [34] (Fig. 26.6). The most important factor that perpetuated FGIDs was anxiety symptoms [34]. Among 703 who completed the follow-up survey, 110 (15.6%) had FD in the first survey, and 93 (13.3%) were diagnosed during the follow-up period, among whom 48 were newly diagnosed cases of FD [34] (Fig. 26.6). Patients with FD commonly had severe anxiety symptoms (OR 6.30; 99% CI, 1.64–24.16), which were closely associated with the EPS subtype of FD in the first survey (OR 4.83; 99% CI, 1.24–18.76) and became more severe during the follow-up (OR 8.12; 99% CI, 2.13–30.85) [34]. Such anxiety symptoms were especially closely related to FD and therefore were associated with the incidence of newly diagnosed FD (OR 7.61; 99% CI, 1.21–47.73), but not with GERD [34], indicating the importance of managing anxiety symptoms to prevent FD. Similarly, the author's research team followed up 494 patients with FGIDs and 239 controls for 75.8 months; symptoms progressed more frequently in the overlap FGIDs, especially in patients with anxiety as well as depression symptoms [33]. When we analyzed genetic poly-

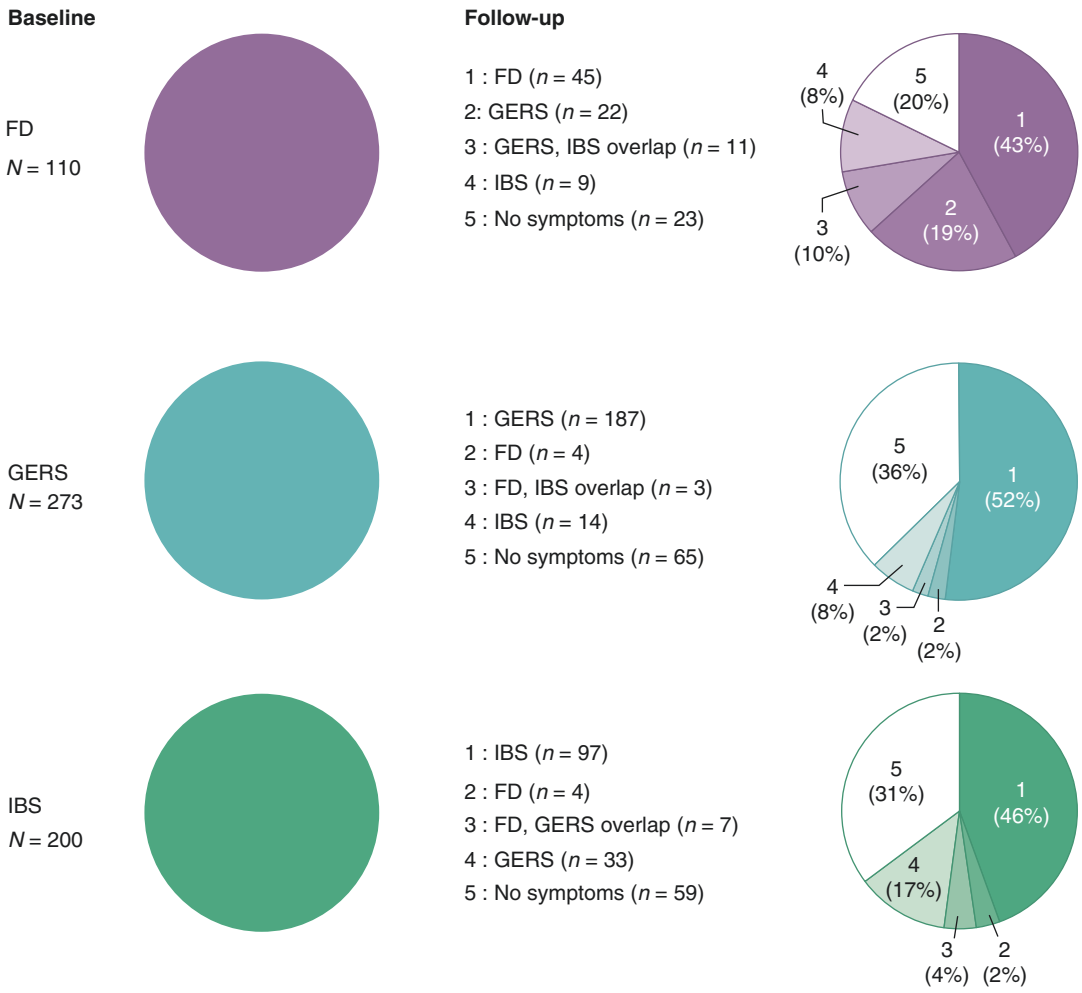

Fig. 26.6 Natural course of FGIDs observed in Sweden for 10 years. Dyspepsia, symptoms of gastroesophageal reflux, and irritable bowel syndrome developed into other FGIDs during the 10-year follow-up, and in the process, overlap occurred frequently. *FD* functional dyspepsia, *GERS* gastroesophageal reflux symptoms, *IBS* irritable bowel syndrome, *FGID* functional gastrointestinal disease (adapted from Aro et al. [34])

morphisms of neurotransmitters which could be associated with certain symptoms of overlap FGIDs, the L/S genotype of the *SLC6A4 5-HTTLPR* gene was also associated with deteriorating symptoms of overlap syndrome [33]. In addition, the 592 C>A polymorphism of the *IL10* gene was associated with symptoms among male patients with IBS (p = 0.009), whereas the *SLC6A4 5-HTTLPR* genotype was closely associated with esophageal symptoms among female patients with FD and IBS, indicating that polymorphisms of genes that affect neurotransmitters contribute to sex/gender differences [33].

Regarding the natural course of FGIDs, data are only available from a few countries [14, 34–36]. The main reasons could be that it is difficult to collect comprehensive surveys since the symptoms of FGIDs are diverse and to find patterns when analyzing the natural course of these conditions. Most studies about FGIDs reported that symptom severity was higher, the impact on QoL was larger, and the incidence of overlap syndrome was higher among females, but since the severity of FGIDs is not as high as that of other diseases, they have not received much attention. It will be important to examine the course of

FGIDs in more detail in the future and to analyze it by sex/gender for efficient treatment.

In some cases, the diagnosis of organic diseases can be delayed due to confusion with FGIDs. The results of long-term follow-up of the incidence of organic diseases in patients with FGIDs showed that around 3% of cases of IBS or FD developed into organic diseases in 6 years [19]. Around 4% of patients with upper GI symptoms had peptic ulcers [3]. In a survival analysis of FGIDs with 30,000 person-years, there were no significant differences in survival rates between the IBS or FD group and individuals without those conditions [37]. It is very different from the mortality due to the complications of peptic ulcer disease such as bleeding [38] and perforation [39]. In contrast, FGIDs have a negligible impact on the incidence of other organic diseases or increased mortality with time, but can decrease the QoL, especially in case of overlap syndrome of FGID.

26.6 Conclusions

FGIDs are common diseases, each of which has a 10–20% prevalence in the general population. It is relatively common to observe more than one FGID in a single patient, and the prevalence of overlap of multiple FGIDs, including GERD, in the general population is around 17%. Overlap syndrome is more common, has more severe symptoms, and lowers the QoL more in women than in men. In terms of the pathophysiology, the overlap in FGIDs occurs due to shared pathophysiology (e.g., visceral hypersensitivity and GI dysmotility) rather than by chance. FGIDs have a negligible impact on the incidence of other organic diseases or increase in mortality, but can become different FGIDs or progress into overlap syndrome with time. The most important risk factor for the persistence of FGIDs was anxiety and depression symptoms [33, 34]. Since anxiety increased the likelihood of long-term persistent FGIDs by 7.6 times, proactive measures to prevent anxiety disorders in the general population are necessary [34]. In addition, genetic factors such as L/S genotype of the *SLC6A4 5-HTTLPR* gene were also associated with deteriorating symptoms of overlap syndrome [33]. More studies about overlap syndrome of FGIDs are needed in the future, especially with a detailed focus on sex/gender differences.

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Part XII

Sex/Gender Differences in Pediatric Gastrointestinal Diseases

27 Sex/Gender Differences in Pediatric Gastrointestinal Diseases

Hye Ran Yang

27.1 Introduction

Sex/gender-specific medicine is an innovative field in recent research, and many studies have been actively conducted in adults. Although it is expected as a major future direction for medical research, there are few related literatures on sex differences in pediatric gastroenterology because it has not yet been well studied in pediatrics.

According to the results of a recent literature review based on a search of the medical database "Pubmed" by "sex (or gender)" and "gastrointestinal (GI) diseases" in "children" under the age of 18, only three papers written in English were published before February 2017 [1]. Since even these sex/gender-specific medicine-related literatures did not properly analyze and present the evidence for gender differences of GI diseases in children and adolescents, sex/gender-specific medicine is still a very limited field in pediatric patients [1].

In anticipation that sex/gender-specific medicine in children and adolescents can be actively conducted in the future, I would like to summarize as much as possible all the content that mentioned sex differences in pediatric GI diseases among the literature published so far and present updated evidence-based knowledge about sex/gender-specific medicine in pediatric gastroenterology.

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27.2 Sex/Gender Differences in Pediatric Gastrointestinal Diseases

27.2.1 Gastroesophageal Reflux Disease

In adult studies, gastroesophageal reflux disease (GERD) is known to be a functional gastrointestinal disorder (FGID) in which the relationship between sex and age has an important influence. In particular, adult women tend to have more common heartburn, reflux symptoms, and extra-esophageal symptoms than men, as well as more non-erosive reflux disease, whereas men are more likely to have pathological conditions such as reflux esophagitis, Barrett's esophagus, and esophageal cancer, showing sex differences [2].

However, studies on gender differences in pediatric GERD have not been sufficiently conducted, and so far, the meta-analysis by Zhang et al. in 2016 that analyzed the prognosis of surgical treatment for GERD is the only study published on gender differences in pediatric patients [3]. According to this meta-analysis, laparoscopic fundoplication for GERD was as effective and safe as open Nissen's fundoplication when a total

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of 3 randomized controlled studies including 171 children were analyzed in the literature published to date [3]. However, the recurrence of GERD and the mortality rate after laparoscopic Nissen's fundoplication from the aspect of the short-term and long-term prognosis were significantly lower in pediatric patients with neurological disorders, in those who underwent surgery at the age of less than 18 months, and female patients [3]. Based on this result, it was suggested that thorough evaluation and preparation were necessary to reduce the risk of surgery and recurrence before considering surgical treatment in these cases at risk [3].

27.2.2 Pediatric Functional Gastrointestinal Disorders

As mentioned before, few studies have analyzed and discussed gender differences in pediatric GI diseases to date [1]. According to the literature on gender differences in pediatric FGIDs by Lewis et al. in 2016, when analyzed by applying Rome III diagnostic criteria to 949 children and adolescents aged 4–18 years, 23.1% of the subjects had at least one of FGIDs and functional constipation was noted in 12.9% as the most common type of FGID in pediatric patients [4]. Of pediatric FGIDs, abdominal migraine was reported in 9.2%, pathological aerophagia in 4.3%, irritable bowel syndrome in 2.8%, encopresis in 1.8%, cyclic vomiting syndrome in 1.1%, functional abdominal pain in 1.3%, and rumination in 0.2% of the study subjects [4]. Even though there were no significant sex differences in most types of FGIDs, functional constipation was observed more frequently in boys than in girls ($p = 0.022$) [4].

27.2.3 Functional Abdominal Pain Disorder

Chronic abdominal pain that persists for more than 2 months is common and doctors often encounter children and adolescents who complain of chronic recurrent abdominal pain in practice because it accounts for 9–15% of children aged 4–16 years. Most of chronic abdominal pain in pediatric patients is functional and abdominal pain due to organic causes is only 10–15%. However, since repetitive abdominal pain interferes with daily life and these children and their parents are worried, appropriate approach and treatment is required.

In a meta-analysis on the epidemiology of functional abdominal pain disorder (FAPD) in children aged 4–18 years old by Korterink et al. in 2015, the prevalence of FAPD in pediatric population was 13.5% (1.6–41.2%) and FAPD was more common in Asia (16.5%) than in Europe (10.5%) [5]. Among the subtypes of FAPD, irritable bowel syndrome was reported as the most common subtype (8.8%) in children [5]. According to this meta-analysis, the prevalence of FAPD was significantly higher in 15.9% of girls compared to 11.5% of boys and the pooled odds ratio was 1.5, indicating a gender difference in pediatric patients [5].

Gender differences in FAPD have been reported all over the world. It is explained that the role of sex hormones is important as one of pathogenesis because sex hormones in female patients may promote GI hypersensitivity to pain and react sensitively to stress [6]. Since young children have not yet reached sexual maturity, this hypothesis applies only to the adolescents [6]. According to previous reports, there were gender differences even in children under 10 years of age before the onset of puberty. This may be because girls tend to express physical symptoms such as pain better than boys and that girls have a lower ability to cope with pain [7].

As for gender difference in the prognosis of FAPD, when Gieteling et al. analyzed prognostic factors of pediatric FAPD in 2011, sex was independent of the duration of chronic abdominal pain and there were no significant differences between girls and boys in terms of clinical course and prognosis [8].

27.2.4 Functional Constipation

Constipation accounts for about 3% of the total pediatric population, 3–7% of pediatric

outpatient clinic, and 25–50% of pediatric gastroenterology clinic. Although many studies have been conducted on the pathogenesis, diagnosis, and treatment of functional constipation in pediatric patients, there are only few studies on gender differences in pediatric constipation.

Based on the results of previous studies, it was suggested that there are sex differences between boys and girls in children with constipation [4, 9]. A meta-analysis study on the epidemiology of childhood and adolescence in 2011 reported that the prevalence of childhood constipation was about 12% (0.7–29.6%) and constipation was observed more commonly in girls than in boys with a ratio of 1:1 to 2.2:1 [9]. According to a study published in 2009 by Pham et al. 44 of 61 (72.1%) constipated children were girls, more than boys [10]. And, boys with constipation were significantly overweight or obese compared to girls, indicating a gender difference [10].

There is a study by Yik et al. published in 2011 on gender differences related to the mechanism of slow transit constipation in children [11]. According to this study, the more common occurrence of slow transit constipation in women than in men was related to the low number of substance P-containing nerve fibers in the circular muscle of the colon [11]. As a result of nuclear transit study and small intestine biopsy of 88 pediatric patients with refractory chronic constipation, 78 children had slow transit constipation and substance P-containing nerve fibers were decreased in 38.5% (10/26) of girls compared to 21.2% (11/52) in boys, indicating that there is a significant gender difference in children with slow transit constipation as in adults [11]. However, in this study, the proportion of female patients with slow transit constipation with reduced substance P-containing nerve fibers in the circular muscle layer of the colon decreased during puberty while the proportion of male patients relatively increased, revealing contradictory results [11]. Therefore, long-term follow-up leading to adulthood would be additionally needed in these patients.

27.2.5 Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis have recently been rapidly increasing in children and adolescents; and various studies related to epidemiology, pathogenesis, diagnosis, and treatment of IBD have been conducted and published to date. However, there are still few studies on gender differences in IBD in children and adolescents.

When looking at several studies on gender differences in IBD in children and adolescents published so far, a study by Thayu et al. in 2007 reported that children and adolescents with CD had lower height and body mass index compared to their age and gender [12]. In particular, it was found that the percentage of body fat was significantly lower in girls than in boys in terms of body composition [12]. According to a study by Herzog et al. in 2014, which analyzed the Swiss IBD cohort of prepubertal pediatric patients under 10 years of age among 196 children with IBD (105 with CD, 91 with ulcerative colitis), the male to female ratio was 2.42 in pediatric CD patients, which was relatively more male, and the male to female ratio in pediatric ulcerative colitis patients was 0.64, which was relatively more female [13]. Thus, there was a significant difference in the ratio of males and females in pediatric patients with IBD under 10 years of age [13]. In the results of this study, the male to female ratio was 1.58 for CD and 0.88 for ulcerative colitis among adolescent patients aged 10 years or older [13]. Furthermore, boys with ulcerative colitis under 10 years of age showed a tendency to delay diagnosis compared to girls with ulcerative colitis, and girls with ulcerative colitis over 10 years of age showed significant gender differences in treatment; e.g., azathioprine was more commonly used as a therapeutic agent in girls than in boys [13]. However, in this study, it was reported that there was no difference between boys and girls in other factors such as age of onset, location of lesions, disease pattern, disease period, family history of IBD, presence of extra-intestinal symptoms, presence of complications, and history of surgery [13].

In addition, according to a study by Gupta et al. on gender differences in the clinical features

and disease course of CD in children, a total of 989 children under the age of 17 (566 boys, 423 girls) were recruited in the pediatric IBD multicenter registry [14]. In a retrospective analysis of pediatric CD patients, there were no gender differences in age or location of lesions at diagnosis, but the presence of oral ulceration and hypoalbuminemia at onset were significantly more observed in girls than in boys [14]. Skin lesions such as erythema nodosum and pyoderma gangrenosum were also more common in girls, indicating that the overall disease course was more severe in females [14]. On the other hand, growth failure in CD in childhood and adolescence was more commonly observed in boys than in girls [14].

Although there are not many studies to date, on IBD in children, there were gender differences in the disease severity and the disease course. More studies related to the gender difference in IBD in children and adolescents are needed in the future.

27.2.6 Congenital Gastrointestinal Anomaly

It is known that some congenital abnormalities show gender differences; however, there are only a few epidemiologic studies in general population [15]. According to previous studies, about 3.9% of boys and 2.8% of girls are born with a major birth defect [16, 17].

As for gender difference of congenital GI anomaly, it has been reported that some congenital anomalies of the GI tract such as cleft palate and congenital pyloric stenosis are more common in boys in up to 61% of patients, showing a significant difference in the prevalence between boys and girls [15]. In particular, according to two representative studies, the relative risk was 1.55 and 1.4, respectively, when comparing the ratio of males and females in severe congenital GI anomalies. For cleft palate, the relative risk was reported to be 1.41 and 1.4, respectively; for congenital pyloric stenosis, 4.43 and 4.6; for congenital megacolon, 2.79 and 2.8; and for anal malformation, 1.7 and 1.37, respectively, indicating male predominance in these diseases [16, 17]. In a recent study on the epidemiology and clinical features of Meckel's diverticulum, the male to female ratio of Meckel's diverticulum was 1.5–4:1, and the incidence rate was up to 4 times higher in boys than in girls, showing a gender differences [18].

27.2.7 Emergency Diseases in Children and Adolescents

It is noteworthy that there are several reports of gender differences in pediatric emergency diseases. According to a study by Salo et al. published in 2015 regarding acute appendicitis among emergency diseases in pediatric surgery, when appendectomy was performed in 427 children under the age of 15, there were more postoperative complications in girls than in boys and more intestinal perforation in boys than in girls [19].

Gender differences have also been reported in intussusception, an important pediatric emergency. According to the results of a nationwide population-based epidemiologic study published in 2020, 34,688 cases of intussusception occurred in 30,444 children under the age of 18 diagnosed with intussusception in South Korean between 2007 and 2017 [20]. As a result of analyzing the big data, intussusception occurred in 28.3/100,000 person-years, and a significant proportion of 83.1% occurred in young children under 3 years of age. Characteristically, there were more males than females in all age groups at 1.39–4.92:1 ratio [20]. As for the treatment of intussusception, the success rate of enema reduction was significantly higher in girls than in boys, and as for the prognosis, there was a difference between boys and girls with an odds ratio of 1.30 for post-discharge recurrence rate of intussusception and 1.23 for operation rate [20].

Since there may be gender differences in treatment and prognosis as well as in the prevalence of emergency disease, it will be helpful to approach pediatric patients by considering gender differences in practice.

27.3 Mechanisms of Sex/Gender Differences in Pediatric Gastrointestinal Diseases

Gender differences in children are caused by various causes such as genetic, biological, and environmental factors. Furthermore, most complex diseases have been described as occurring as a result of changes caused by differences in genetic background and interactions with the external environment and these interactions are regulated by mediators such as various hormones from the fetus in the uterus to the adolescence [15].

27.3.1 Sex Hormone

The transition of each developmental period in children and adolescents is accompanied by characteristic changes in hormones, and the role of sex hormones and sex hormone receptors is considered to be particularly important [15].

Gender differences start in the womb. In the fetus, the fetal-placental unit can convert cholesterol to pregnenolone between 6 and 12 weeks of gestation, allowing the fetal adrenal gland to produce dehydroepiandrosterone (DHEA) and DHEA sulfate. DHEA and 16α-OH-DHEA are converted into androgen, a male hormone, and androgen is converted into estrogen, a female hormone, under aromatization by cytochrome P450 aromatase [21]. These hormone differences between male and female not only affect the reproductive organs but also affect the formation and development of the brain and the lung and, furthermore, have an impact on fetal programming in the womb, which is known to be associated with adult diseases. It may also contribute to gender differences in diseases later in life.

After birth, blood levels of sex hormones originating from the placenta decrease, while serum levels of follicle stimulating hormone and luteinizing hormone increase. In boys, there is a surge of serum testosterone during the first few months after birth, and then after 6 months of age, serum levels of gonadotropins decrease to the low levels that are present before the beginning of puberty [15]. In girls, estradiol increases during the first year, and the blood gonadotropin concentration decreases until the onset of puberty. At the age of 8–9, just before puberty, in girls, the estrogen concentration begins to increase and, moreover, androgen metabolites are also high [22].

During puberty, a surge in sex hormone secretion causes pubertal changes in adolescents and maturation of the reproductive system. Sex hormones can cause dysregulation of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axis. Stressors may activate neuroendocrine axis producing cortisol which orchestrates the immune responses, and estrogen stimulates the hypothalamic-pituitary-adrenal axis through corticotrophin releasing hormone that, in turn, abolishes the action of gonadotropin releasing hormone inducing a drop of sex hormones [15]. It is known that girls respond better to immune stimuli than boys, and girls produce more innate and humoral immune responses than boys [15, 23, 24].

These hormonal differences can cause gender differences between boys and girls according to developmental stages, which can also indicate gender differences in the pathogenesis of some pediatric diseases.

27.3.2 Sex Chromosome

The gender difference between male and female in children and adolescents can be fundamentally due to differences in sex chromosomes. That is, sex differences may appear regardless of the action of sex hormones for each developmental period, which can be attributed to the direct influence of genes encoded in sex chromosomes [15]. These include genes on the Y chromosome, genes that avoid inactivation among genes on the X chromosome, and genes imprinted in the paternal line that function in some XX cells [25]. In general, it is considered that both genetic and environmental factors contribute to the development of congenital anomalies and complex diseases in children and adolescents [26].

27.3.3 Environmental Factors

Environmental influences also work together in the gender difference in pediatric diseases. Some toxic substances along with various environmental factors may cause epigenetic changes that make a difference in gene expression in children, affecting the onset of various diseases, and thus may act as a risk factor. In particular, when exposure to risk factors during the prenatal, perinatal, and neonatal period, which is the critical window for sensitively responding to these environmental factors, fetal programming and postnatal programming may occur, and environmental factors can affect the onset of diseases and cause various diseases [15]. Gender can also influence gene-epigenetic interactions, and thus these interactions may contribute to gender differences in the pathogenesis of childhood and adolescence diseases [27].

27.4 Conclusions

As mentioned above, although there are gender differences in various GI diseases in children and adolescents, studies in this field are still insufficient. As a pediatric gastroenterologist, I hope that many researchers will be interested in sex/gender-specific medicine in the field of pediatric gastroenterology and hepatology and conduct in-depth research on more diverse pediatric GI diseases to lay the foundation for sex/gender-specific medicine in children and adolescents in the future.

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Part XIII

Pharmacokinetics and Pharmacodynamics of Gastrointestinal Drugs

28 Pharmacokinetics and Pharmacodynamics of Gastrointestinal Drugs

Seonghae Yoon

28.1 Introduction

First, we'll review the concept of pharmacokinetics (PK) and pharmacodynamics (PD) and possible causes of sex differences in PK and PD.

28.1.1 Pharmacokinetics and Pharmacodynamics Concepts

A drug is absorbed into the systemic circulation from the administration site and then goes through the distribution process to reach the effect site, and at the same time, the drug is eliminated from the body through the kidneys and liver [1]. This whole process is called the pharmacokinetic process [2] (Fig. 28.1). After that, the drug reaching the site of action exhibits effects through drug-receptor interaction in what is called the pharmacodynamic process. Thus, PK can be said to be the process by which our body handles drugs, and PD can be said to be the process by which drugs affect our body.

The strength and duration of pharmacological responses are determined by PK (e.g., changes in the pattern of plasma drug concentrations) and PD properties (e.g., the sensitivity of the receptor) of the drug. Variability in drug responses is due to individual differences in PK and PD [1]. Factors such as the patient's age, weight, disease status, concomitant medications, environment, genotype, and sex/gender may be the cause of these differences [1] (Fig. 28.2), and this chapter will mainly focus on sex/gender differences.

28.1.2 Pharmacokinetic and Pharmacodynamic Differences by Sex

Men and women show structural, morphological, and physiological differences in various organs; and these differences can affect the PK and PD of drugs [3, 4]. PK differences may occur due to physiological differences (Table 28.1), and it is necessary to adjust the dose or administration interval of the drug in consideration of these differences [5]. It is more important to consider these variations in drugs with a narrow therapeutic range, such as warfarin.

28.1.2.1 Absorption

For a drug to be absorbed into the body, it must pass through biological membranes in the gastrointestinal (GI) tract, skin, and respiratory system, and men and women show differences in these organ characteristics.

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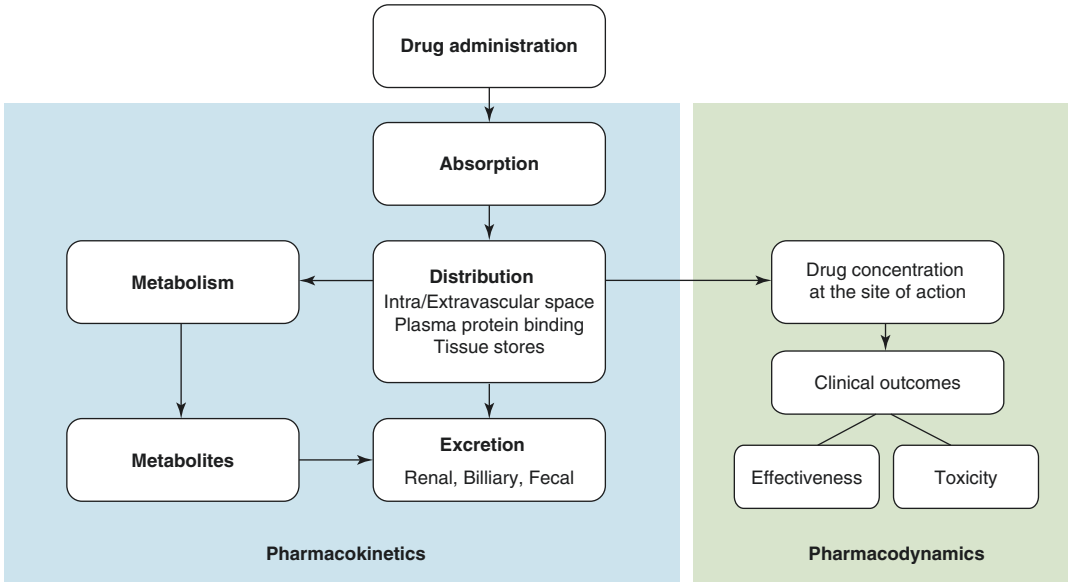

Fig. 28.1 Pharmacokinetic and pharmacodynamic processes. A drug undergoes absorption, distribution, metabolism, and excretion processes (pharmacokinetic process) and reaches the site of action to exert drug effects. Clinical effects can be divided into clinically expected effects and non-toxic effects (adapted from Tamargo et al. [2])

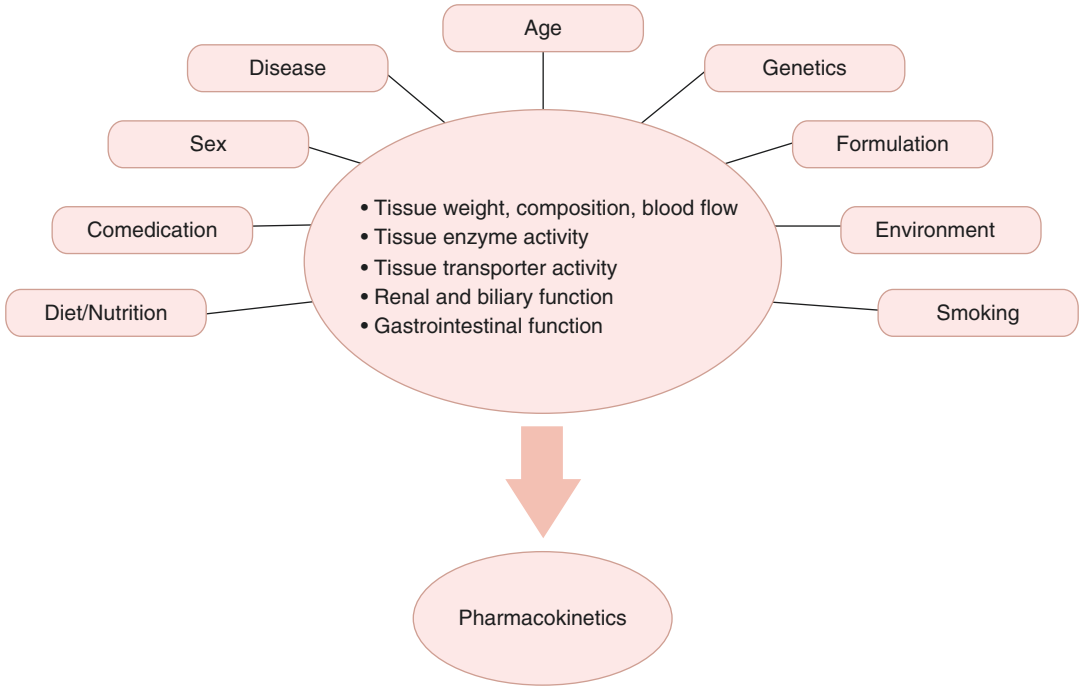

Fig. 28.2 Factors influencing pharmacokinetic variability (adapted from Harmut and Stephan [1])

Women secrete less gastric juice than men (pH is about 0.5 higher in women), and the GI transit time is longer than in men. When the gastric pH is high, the absorption of drugs whose dissolution degree varies depending upon pH may be affected. Also, due to slow GI emptying

Table 28.1 Pharmacokinetic factors and their influencing physiological sex differences (adapted from Tamargo et al. [2])

Pharmacokinetic factors		Sex differences
Bioavailability	Gastric acid secretion	M > W
	Gastrointestinal movement	M > W > P
Body composition	BSA (body surface area)	M > P > W
	Organ size	M > W
	Organ blood flow	Blood flow to skeletal muscle and liver is greater in men. Blood flow to adipose tissue is greater in women
	Body water	M > P > W
	Plasma volume	P > M > W
	Body fat percentage	W > M
Distribution	Volume of distribution	Hydrophilic drug: M > W Lipophilic drug: W > M
Drug excretion	Renal blood flow	M > W
	Glomerular filtration rate (GFR)	M > W

M men, *W* women

in women, the absorption of drugs in the small intestine may be delayed. Therefore, when taking drugs such as tetracycline and felodipine, which should be taken on an empty stomach, women may need a longer fasting time.

Intramuscular and subcutaneous injections may also show differences between men and women because women have more subcutaneous fat. For example, when cefradine is injected into the gluteus muscle, the absorption rate is slowed and bioavailability is reduced in women. As a result, the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) are reduced [6, 7].

28.1.2.2 Distribution

The distribution of drugs varies depending upon the physicochemical properties of the drug, blood flow, and body composition. Compared to women, men have higher body and organ weight, more muscle mass, and less body fat. Because women generally have more body fat, the volume of distribution (Vd) of lipophilic drugs (e.g., benzodiazepines) is greater and the half-life is longer. In contrast, hydrophilic drugs (e.g., alcohol and fluoroquinolone antibiotics) have a small Vd in women.

Adjusting the dose according to body weight can help reduce the variations due to body composition and size. Also, when determining a loading dose or bolus dose, it may be necessary to use a lower dose to prevent side effects in women. Medications such as aminoglycosides, anticancer drugs, digoxin, heparin, lidocaine, and class I or III antiarrhythmic drugs may require loading dose adjustment in women.

28.1.2.3 Metabolism

Many drugs are metabolized in the liver and then excreted. In addition to sex, various factors including liver disease can influence the degree of metabolism. Metabolism is divided into phases 1 and 2, both of which may differ between men and women. The cytochrome P450 (CYP) enzyme system, which accounts for a significant portion of phase 1 metabolism, metabolizes a variety of endogenous and exogenous substances. Among the CYPs, CYP1A2, CYP2D6, CYP2E1, and CYP3A4 are known to show sex differences [6, 8, 9] (Table 28.2).

CYP2D6 is more highly expressed in men, and the clearance of its substrates is also increased. Various antiarrhythmic drugs and beta-blockers are metabolized by CYP2D6. In the case of beta-blockers metabolized mainly by CYP2D6, the incidence of adverse drug reactions is also higher in women due to higher blood drug concentrations. CYP3A4 is mainly expressed in the liver, and it contributes 50% of the metabolism of atorvastatin, diltiazem, quinidine, verapamil, simvastatin, nifedipine, amlodipine, and lidocaine [10]. Nifedipine, verapamil, and amlodipine showed greater drug clearance in women than in men (about 15–35%) even after adjusting for bodyweight [10, 11].

Table 28.2 CYP450 enzymes and sex differences in hepatic metabolism (adapted from Kalibala [9])

CYP	Enzyme activity	Hormonal influence
1A2	M > W	Inhibited by oral contraceptives
2A6	W > M	Induced by estrogens and oral contraceptives
2B6	W > M	Induced by estrogens and oral contraceptives
2C9	M≒W	
2C19	M≒W	Inhibited by oral contraceptives
2D6	Mostly W > M	
2E1	M > W	
3A4	W > M	Induced by testosterone and progesterone

CYP cytochrome P450, *M* men, *W* women

28.1.2.4 Excretion

Drugs and their metabolites are excreted through the kidneys, gallbladder, and lungs; and among them, renal excretion is important. The extent of renal filtration, secretion, and reabsorption may differ between men and women; and the glomerular filtration rate, estimated using creatinine clearance, is greater in men. For drugs that are primarily excreted by the kidneys, drug clearance is proportional to renal function. Therefore, in the case of drugs that are mainly excreted by the kidneys, such as digoxin, the drug clearance rate may be lower in women.

28.2 Sex Differences in Pharmacokinetics and Pharmacodynamics of Gastrointestinal Drugs

Although few studies have directly compared the differences in the PK and PD of GI drugs between men and women, the results are summarized below by disease.

28.2.1 Gastroesophageal Reflux Disease

Among the drugs used for gastroesophageal reflux disease (GERD), lafutidine, an H2 blocker, showed significantly higher maximum plasma concentrations (C_{max}) and trough concentrations (C_{min}) in women after repeated administrations. The C_{max} and AUC were found to be 34% and 23% higher in women, respectively [12].

In the case of PPIs, the results were somewhat different for each drug. There is no description of sex differences in the drug label for omeprazole, but the drug label for rabeprazole stated that there is no difference in PK between males and females. Both sex and the CYP2C19 genotype were demonstrated to affect the PK of omeprazole [13]. The concentrations of both omeprazole and its metabolites were higher in women. The AUC was ~30% and the C_{max} was ~50% higher. When ilaprazole was administered intravenously, the C_{max} was ~10% and the AUC was ~30% higher in women, which led to PD differences. In the ilaprazole 5 mg or 10 mg dose groups, women maintained a higher average pH in the 24-h esophageal pH monitoring test, but these differences were not evident at 20 mg [14] (Fig. 28.3).

Several studies showed that the proportion of patients with persistent symptoms despite PPI use was higher in women [15–17]. According to a post-hoc analysis of the LOTUS study [18], in patients taking 20 mg esomeprazole, women, smokers, patients without *Helicobacter pylori* infections, and patients with a long history of GERD may need a higher dose. In contrast, a study showed that halving the dose in female patients was more successful in patients who had been using PPIs for a long time (>2 years) [19].

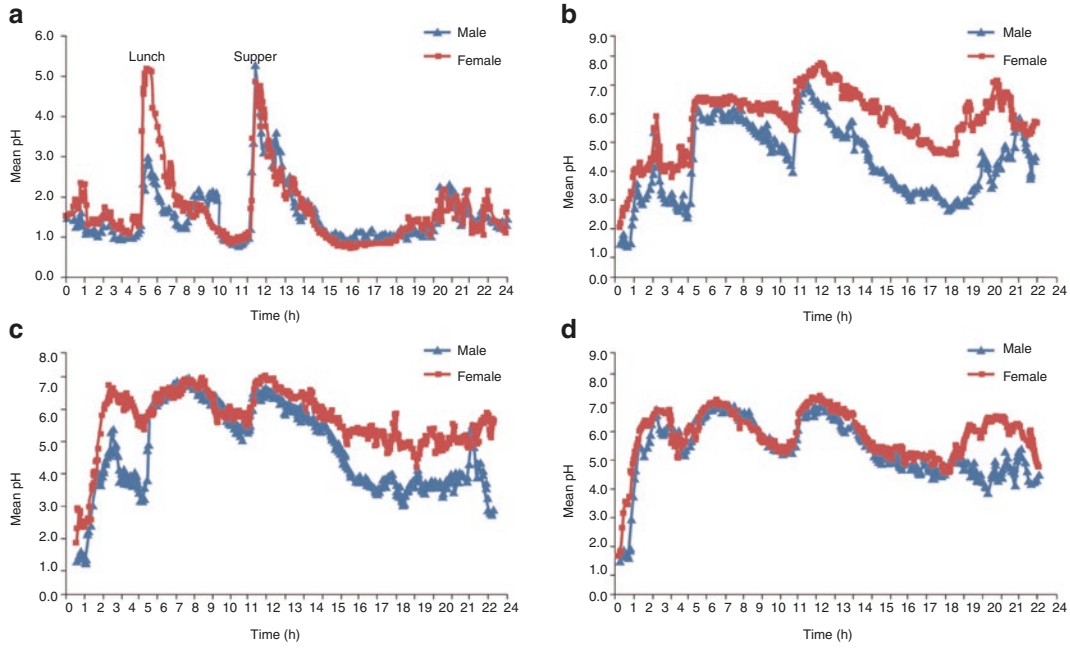

Fig. 28.3 Mean 24-h intragastric pH-time profiles of male and female subjects before and after the intravenous infusion of ilaprazole at (**a**) baseline and (**b**) from 5 mg, (**c**) 10 mg, and (**d**) 20 mg administrations (adapted from Wang et al. [14])

Combining these research results, it seems that the treatment success rate was higher in men due to complex factors such as the pathophysiology of the disease and the mechanism of action of the drugs. However, in women who respond to the drug, the effect may be maintained even if the dose is reduced because the drug concentration is higher than in men.

28.2.2 Functional Dyspepsia

According to a study evaluating the PK of levosulpiride, the half-life of an intramuscular injection was somewhat longer in women, but there was no significant difference in drug exposure [20, 21]. In the case of the oral formulation of metoclopramide, no study has compared sex differences. In the results of a phase 2 clinical trial of metoclopramide nasal spray formulation in diabetic gastroparesis patients [22], there was no difference in drug concentrations between men and women. Nevertheless, while women showed improvements in symptoms, male patients did not show symptom improvement compared to the placebo group. This formulation was recently (June 2020) approved by the U.S. Food and Drug Administration (FDA) for symptom relief for acute recurrent diabetic gastroparesis.

28.2.3 Liver Disease

Ribavirin is a drug used to treat chronic hepatitis C. Although it is stated on the drug label that there is no sex difference in PK, population PK studies showed that some PK parameters of ribavirin were different between men and women [23–25]. Studies have shown that there is a difference in the peripheral volume of distribution (Vp) or apparent clearance (CL/F) [24, 25]. According to the results of a population PK and

PD analysis [25], body weight, sex, age, and creatinine affected the CL/F. The steady-state blood concentration (C_{ss}) was higher in women, and the CL/F calculated according to the following equation was lower in women.

$$\frac{\mathrm{CL}}{\mathrm{F}} = \mathrm{Dose} / \left(C_{ss} \times 24\right)$$

The polymerase chain reaction (PCR) response rate of hepatitis C virus (HCV) was affected by the virus genotype, the HCV-RNA titer before treatment, the treatment period, the ribavirin concentration at 4 weeks, and the patient's age. Higher ribavirin concentrations at week 4 were associated with a higher response rate, suggesting that treatment success rates might be higher in women.

In studies that mainly evaluated the treatment effects, the results differed from study to study [26, 27]. In a study in which peginterferon and ribavirin were administered in combination, the effect (sustained virologic response (SVR)) was lower in blacks than in non-Hispanic whites, while there was no difference between men and women [26]. Another similar study found that race (more effective in whites), sex (more effective in women), baseline virus levels, liver fibrosis scores (Ishak fibrosis score), and peginterferon dose were associated with SVR [27]. There may be differences between men and women in the incidence of adverse reactions as well as the treatment effect. Hemolytic anemia is one of the major adverse drug reactions of ribavirin and occurred in ~13% of the patients in major studies such as COPEGUS and PEGASYS [28]. According to one study, the incidence of anemia was significantly different between men and women (48.2% for women, 13.3% for men), and symptoms such as anorexia, dizziness, and nausea were also found to be more frequent in women [29].

A population PK analysis study of triple direct-acting antiviral therapy [30] confirmed that sex was an important covariate of the CL/F of all drugs used in the study. The exposure of paritaprevir, ombitasvir, and ribavirin was increased in women by ~1.9, 1.5, and 1.3 times, respectively (Fig. 28.4).

28.2.4 Colon Disease

In the case of alosetron, a drug for irritable bowel syndrome (IBS), the C_{max} and AUC of the oral formulation were ~50% higher in women and these differences were larger in elderly men and women [31]. In addition, a bioequivalence study confirmed that the C_{max} was about 70% higher in women [32].

Alosetron was more effective than the placebo in both men and women, and the effect was more evident in women, but it is difficult to explain these differences in effect only by the differences in drug concentrations [33].

Naloxegol, a drug for constipation, showed no PK difference between men and women in a study of healthy volunteers, and the C_{max} and drug exposure levels were not significantly influenced by sex even though it was a significant covariate for Vd in a population PK study that included patients [34, 35].

28.3 Conclusions

Drugs reach the site of action through ADME processes to show drug efficacy, and there may be differences between men and women in these PK and PD processes. To obtain an appropriate drug effect in both men and women, it is crucial to understand these differences and optimize therapy. Therefore, studies that consider these differences between men and women from the drug development stage are necessary.

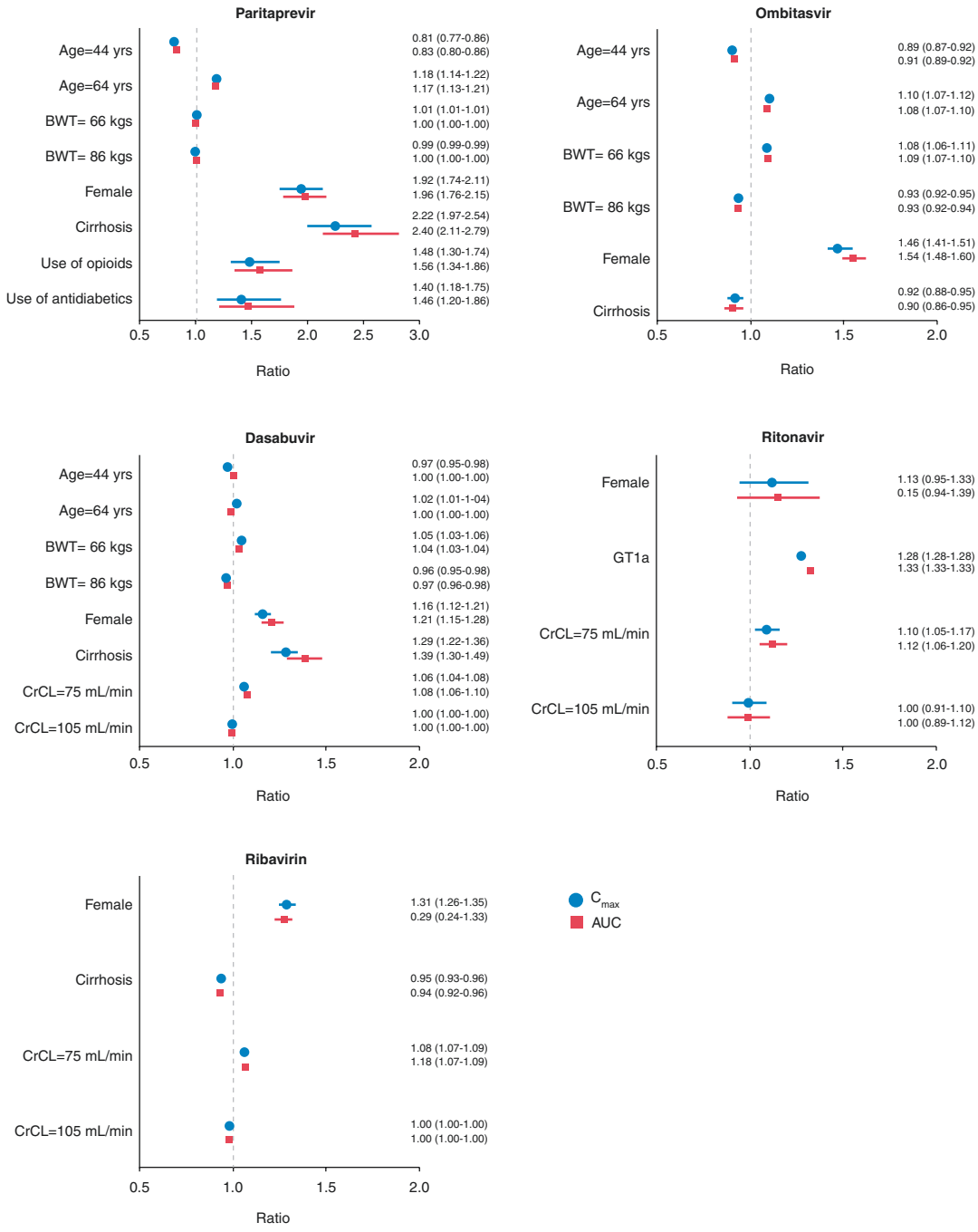

Fig. 28.4 Model-derived estimates of steady-state maximum plasma concentrations and AUC for significant covariates identified in a triple direct-acting antiviral regimen. Using the developed model, the maximum drug concentration ($C_{max,ss}$) and area under the blood drug concentration-time curve (AUC_{ss}) at steady-state were predicted according to significant covariates. A value of 1.0 indicates no significant difference between the groups, and the error bar indicates the 95% confidence interval (adapted from Mensing et al. [30])

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Part XIV

Importance of Education in the Sex/Gender-Specific Medicine and Work-Life Balance of Korean Gastroenterologists

29 Importance of Education in the Sex/Gender-Specific Medicine

Nayoung Kim

29.1 Introduction

Sex/gender-specific medicine is defined as the practice of medicine based on the understanding that biology and social roles are important in men and women for prevention, screening, diagnosis, and treatment [1]. This concept has been well explained in a book entitled *Sex and Gender Aspect in Clinical Medicine* [2]. Medicine in the twenty-first century is characterized by an ongoing rapid and global increase in knowledge and understanding of human health and disease as well as progressive discussions on how best to approach them [3]. This medical progress should continuously be evaluated regarding its relevance for incorporation into undergraduate medical curricula. Diversity issues such as sex/gender, age, culture or ethnicity, religious beliefs, sexual orientation, and disabilities represent one area of major changes in knowledge which has impacted medicine in recent years [4, 5]. Furthermore the advent of competency-based medical education is transforming postgraduate medical education to an outcomes-driven education and assessment model [6]. Key elements of the competency-based medical education approach include a focus on enhanced competencies with the goal of improving patient outcomes; the use of milestones and entrustable professional activities to provide a structure for teaching, learning, and assessment; and the use of time as a resource for learning rather than as a proxy for progression of competence [7]. Taken together, it is important to understand that sex/gender-specific medicine is part of the move toward precision medicine.

Existing research demonstrates differences in disease incidence, symptomatology, morbidity, and mortality based on sex/gender [8]. Thus, both variables must be considered in medical education and practice as well as in research. Integration of sex and gender medical education (SGME) into core medical curricula is essential to achieve competency-based continuing professional development for medical doctors and researches. Experiences about SGME on many Western countries including the United States, Germany, and other European countries, have been reported recently with the formats of reviews, summits, and surveys. In addition, many participants express their experience like that SGME is important for clinical practice in various fields of medicine [3]. However, the impact of SGME on their clinical practice looks limited mainly because it has not been pertained to specialty. To establish SGME as fundamental curriculum, supporting system, educational materials, structured modules, case studies, and reports about experiences are much more needed [1, 2]. In this chap-

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t e r , SGME experiences in the Charité—Universita¨tsmedizin Berlin in 2010 [3] and in several fields such as training in Women's Gastrointestinal (GI) Health [9] and training to reduce lesbian, gay, bisexual, transgender, and questioning (LGBTQ)-related bias [10] and our experiences of SGME for postgraduate course and medical students in Seoul National University College of Medicine [11] are introduced.

29.2 A Successful Strategy to Integrate Sex/Gender Medicine into a Newly Developed Medical Curriculum in the Charité—Universita¨tsmedizin Berlin

Undergraduate medical education has some tendency to stereotype patients through the study of presenting clinical signs and symptoms, yet it is evident that diversity issues have an important influence on the prevention, development, diagnosis, clinical presentation, progression, and treatment of diseases. These diversity issues can also lead to different health behavior, including the acceptance of preventive measures, and therefore require adequate knowledge and skills from medical doctors in the diverse areas [12–16]. Since sex/gender-specific medicine is rapidly growing in respect to knowledge and importance [17], the implementation of the content and modality of sex/gender-specific medicine is necessary for the development of novel strategies for undergraduate medical education [18–22] (In this section the author is referring to Ludwig et al. [3]).

29.2.1 Integration of Sex/Gender-Specific Medicine in the Medical Curricula

The inclusion of sex/gender medicine into undergraduate medical curricula has started recently and has already made progress in several countries [3]. In Europe, for example, Radboud University in the Netherlands [23, 24] Umea University [25], and the Karolinska Institute [26] in Sweden as well as several universities in Austria [27] have made significant efforts to integrate sex/gender aspects into their existing curricula. These efforts improved the gender awareness of future medical doctors [28]. Also, in Canadian [19, 20, 29, 30] and American [31–33] medical schools, sex/gender-sensitive curricula are being developed [34]. Verdonk et al. developed the catalogue of characteristics for a successful integration of gender into a medical curriculum of the University of Nijmegen [23] and then for a Dutch national project [35] and developed the Nijmegen Gender awareness scale that was used in a study with Dutch and Swedish medical students [36]. Dielissen et al. have also developed a teaching program in gender-specific medicine for general practice training [37].

29.2.2 Establishing a Supporting Organizational Framework for Incorporating Sex/Gender Medicine into the New Curriculum in the Charité—Universita¨tsmedizin Berlin

In 2010, a large European medical faculty, the Charité—Universita¨tsmedizin Berlin, started to enroll all new medical students into a new medical curriculum [3]. This curriculum has been sequentially (i.e., module and term-wise) planned and implemented with a standardized, systematic, and faculty-wide approach [3]. Along with the fundamental curricular changes, the faculty directors assigned a change agent to achieve this mission [3]. The final aim was to foster the students' ability to apply the gender perspective as an important tool to improve their diagnostic, clinical, and treatment skills as well as communication abilities with the patients [3]. The consideration and knowledge of sex/gender differences in the development, diagnosis, and treatment of diseases results in a more personalized, cost-effective, and better quality of medical

care for men and women [8]. Since both the medical treatment and the interaction between the doctor and the patient are highly influenced by gender [38–41], the students need to be aware that gender roles and gender stereotypes are important aspects that can affect their professional activities [42]. Many diseases, like thyroid gland disorders [43], for instance, and various cancers follow different patterns depending on the patient's sex [44]. Gender as the psychosocial and the cultural determinant of the sex of the patient is an important predictor of many attitudes and behaviors that have an impact on health and disease [45]. Several studies have shown that communication can lead to different treatment decisions depending on the gender/sex of the patient or doctor [39]. For example, women are more likely to receive prescriptions during a visit to the physician, are more often prescribed psychotropic medication, and spend more money on prescription and nonprescription drugs in general [46].

From this background, Verdonk et al. proposed a standard for the integration of sex/gender-specific medicine and gender aspects in undergraduate medical education [23]. This includes: (1) a list of diseases and issues with sex/gender differences which are to be recognized and explained including risk factors, prevention, development, diagnosis, progression, and treatment of diseases; (2) the incorporation of gender differences into the final block objectives; (3) an education that focuses on both biomedical and sociocultural differences; (4) an education on gender differences over the course of several study years (minimum of 2 years); (5) a coverage of at least six to eight blocks of the central curriculum; and (6) the opportunity to select one optional block on sex/gender issues. For the effective implantation of this integration of sex/gender-specific medicine, following questions have been addressed: (1) How could sex/gender medicine issues be integrated into the different teaching formats of the new curriculum and what factors played a role? (2) Was the integration successful?

The key to the organizational framework was the placement of the change agent directly into the project management team in charge of the curricular development process of the new curriculum [3]. The project management team consisted of an interdisciplinary group of curriculum developers and works in close and constant communication with (1) faculty delegates from all disciplines and departments; (2) centrally located educational experts for e-learning, problem-based learning, communication training, evaluation, and assessment; and (3) members of the faculty directory, especially the dean of student affairs [3]. By being part of this team, the change agent participated regularly in the module planning process and thus could ensure that diversity perspectives, especially sex/gender-specific medicine aspects, were taken into consideration in all important decisions during each step of the curricular planning process. Furthermore the work of the change agent was supported by three pillars: governance, faculty, and society [3].

29.2.3 Barriers in New Curriculum of Charite´– Universita¨tsmedizin Berlin

During the curricular integration of sex/gender medicine aspects within the framework of the Charité—Universita¨tsmedizin Berlin study Ludwig et al. [3] experienced several barriers. One barrier involved some resistances from faculty members toward this subject [3]. However, in many cases this could be overcome by the change agent through qualified arguments to explain the integration and the provision of research findings on sex/gender differences in diseases [3]. The second barrier was the limited curricular teaching time available in the curriculum and the competition of all disciplines to place their contents [3]. This problem was partly approached by deciding to integrate the selected sex/gender medicine issues into other subject courses over the whole curriculum. The third barrier was that the planned courses were not always

taught by the actual course planners who were present in the module planning sessions and responsible for the course conception, but rather by other faculty members of their respective institute or clinic. In some cases, partly due to insufficient briefing by the course planner, those lecturers did not teach the integrated sex/gender medicine aspects as originally foreseen. Finally, a concern may be the sustainability of the integrated sex/gender medicine aspects in the absence of change agent [3]. However, the establishment of a quality control process linked to the periodic module review cycles and the curricular academic board as well as a network of sex/gender medicine experts within the faculty participating in the periodic module review cycles and the approval of curricular changes by the curricular academic board would contribute to the sustainability of the integrated aspects [3].

29.3 Training in Women's Gastrointestinal Health

Women's GI health is a topic that is not well understood nor taught in most training programs. The first step in the process of incorporating it in education is to identify and acknowledge the differences in disease presentations and management between men and women [9]. For example, women experience slower emptying from the large intestine and consequently have a higher prevalence of chronic constipation [9]. In addition, women are almost twice as likely to be diagnosed with irritable bowel syndrome (IBS) and more likely to exhibit the constipation-predominant subtype and postprandial distress syndrome subtype functional dyspepsia [47, 48]. It is well known that hormonal changes during menstruation, pregnancy, and menopause have physiological effects on the GI tract. Clinicians have to evaluate the possibility of conditions unique to pregnancy and choose the best therapeutic strategy, keeping in mind options that are of low risk to the fetus [9]. Recognition of not only diseases but gender differences in laboratory values, diagnostic tests, and the pharmacokinetics of medications is also key to optimized patient management. Gastroenterologists, fellows as well as residents, and medical students need to have proper training in women's GI health to identify some common conditions to provide the best possible treatment for their female patients (In this section the author is referring to Lakshmanan et al. [9]).

29.3.1 Patient Care

Quality of medical healthcare is often assessed based on the patient's relationship with medical doctors and satisfaction with meeting expectations [9]. However, a female patient may be less likely to discuss her bowel habits or seek medical care for delicate problems such as fecal incontinence unless she is in a comfortable setting. This example shows the importance of having gastroenterologists and fellows recognize the gender differences that underlie seeking medical care [9]. Multiple studies have suggested that female patients prefer female endoscopists and are willing to wait for their procedures until one becomes available [49–51]. Women face added challenges during endoscopies, particularly colonoscopy. They tend to have longer and more tortuous anatomy, and those who previously underwent hysterectomy or other pelvic surgeries may be predisposed to adhesions, complicating the procedure [9]. For example, there were sex differences in Boston bowel preparation score, cecal intubation time, and withdrawal time for subjects undergoing colonoscopy [52]. Women are also less compliant with colorectal cancer screening and less likely to be referred by their primary care physicians compared with breast or cervical cancer screenings [50, 51, 53]. In addition, studies have shown that women tend to underestimate the risk of colorectal cancer, despite the fact that it is the second most common malignancy in women [53, 54]. In a survey conducted by Bocci et al. [53], women reported greater embarrassment to undergo a colonoscopy compared with a PAP smear. Furthermore, more than 40% of women felt awkward even

when the colonoscopy was performed by a member of the same sex [53].

29.3.2 Training for Women's Health Issues in Digestive Diseases Regarding Pregnancy

In 2003, the Gastroenterology Leadership Council mandated training in women's health issues in digestive diseases as part of the Gastroenterology Core Curriculum [47]. However, inadequate guidance and implementation, lack of exposure to appropriate patient populations (e.g., pregnant patients), deficits in knowledge in this field at the faculty level, and poor multidisciplinary collaboration prevent some programs from meeting these specific training goals [55]. A better understanding of GI and liver disease effects on fertility and pregnancy will help deliver better subspecialty care for women [9]. Common pregnancy-related problems such as heartburn (present in 80% of pregnant women) require vast and deep knowledge of drug safety and the pathophysiology of gastroesophageal reflux disease (GERD). For more potentially serious problems such as abdominal pain, one needs a deeper understanding of the causatives and time of occurrence during pregnancy [9]. Most pregnancy-related mild GI symptoms such as vomiting and constipation are managed by the obstetrician [56]; however, gastroenterologists should be aware of certain serious complications. GERD and inflammatory bowel disease (IBD) may be exacerbated during pregnancy and IBD may be associated with worse pregnancy outcomes, even during quiescent disease [57, 58]. Abortion and preterm birth may happen during active disease, whereas there is an increased risk of preterm birth, stillbirth, and low birth weight during IBD exacerbations [56]. Therefore, it is advised that women with IBD have a 3- to 6-month period of sustained remission before conception [57]. Active IBD during pregnancy should be treated, as inflammation poses a higher risk to the fetus compared with the side effects of medications. During pregnancy, most treatments can be used except methotrexate and thalidomide, as they are teratogenic [59]. Regarding biologic agents such as infliximab, the latest European Crohn's and Colitis Organisation consensus recommends stopping antitumor necrosis factor therapy in the last trimester, but other studies have demonstrated a benefit in maintaining treatment through all trimesters [60]. Hepatobiliary disorders unique to pregnancy include intrahepatic cholestasis of pregnancy, hemolysis, elevated liver enzymes, low platelet count syndrome, and acute fatty liver of pregnancy [9]. A recent study highlighted that women with maternal Hepatitis B surface antigen-positive status may have a higher risk of gestational diabetes, intrahepatic cholestasis of pregnancy, preterm birth, and neonatal asphyxia [61]. Meanwhile, acute hepatitis E infection compared with other hepatotropic viral infections was found to be more virulent during pregnancy, causing frequent progression to fulminant hepatic failure with a mortality rate of up to 10–20% [62]. Unfortunately, treatment remains supportive, and the best approach is through prevention [62]. Endoscopy is considered low risk during pregnancy for appropriate indications, and all elective procedures are deferred until after delivery [9]. Upper endoscopy with epinephrine injection, thermocoagulation, sclerotherapy, and endoscopic band ligation are safe and successful procedures during pregnancy [63]. Sigmoidoscopy is generally performed to evaluate major lower GI bleeding, suspicion of colonic mass, and severe persistent diarrhea with unknown etiology [63]. Colonoscopy, in contrast, is only performed if necessary for diagnostic or therapeutic decisions [9]. Endoscopic retrograde cholangiopancreatography is usually avoided due to radiation exposure to the fetus; however, endoscopic ultrasonography can be done to reduce unnecessary interventions in patients who have a lower or moderate probability of choledocholithiasis [63]. Estrogen and progesterone levels change during menstruation, pregnancy, and menopause, which affect the GI tract and liver function, and may worsen pre-existing functional

disorders such as GERD and IBS [9]. The involvement of estrogen in visceral pain processes is complex, as estrogens drive both pro- and antinociceptive pathways that affect abdominal pain perception in women and quality of life in disease states [64]. This basic information suggests that further research is necessary for the training for women's health issues in digestive diseases regarding pregnancy.

29.4 Training to Reduce Lesbian, Gay, Bisexual, Transgender, and Questioning (LGBTQ)-Related Bias

LGBTQ individuals experience higher rates of health disparities. These disparities may be driven, in part, by biases of medical providers encountered in health care settings [10]. Little is known about how medical, nursing, or dental students are trained to identify and reduce the effects of their own biases toward LGBTQ individuals, so far (In this section the author is referring to Morris et al. [10]).

29.4.1 Health Care Needs of LGBTQ Patients

LGBTQ individuals represent a rapidly growing segment of the US population [65]. Implicit physician biases could result in LGBTQ patients receiving a lower standard of care or restricted access to services as compared to the general population [66]. Even when institutions and providers make commitments to equitable care explicit, implicit biases operating outside of conscious awareness may undermine that commitment [10]. There is an urgent need to ensure that health care providers are prepared to identify and address their own implicit biases to ensure they do not contribute to the health care disparities experienced by LGBTQ and other vulnerable populations [10]. It has been reported that LGBTQ individuals face significant disparities in physical and mental health outcomes [67]. Compared to their heterosexual counterparts, LGBTQ patients have higher rates of anal cancer [68], asthma, cardiovascular disease [69–72], obesity [70], substance abuse [72–74], cigarette smoking [75], and suicide [76]. Sexual minority women report fewer lifetime PAP tests [77–79], transgender youth have less access to health care [80], and LGBTQ individuals are more likely to delay or avoid necessary medical care [81] compared to heterosexual individuals. These disparities are due, in part, to lower health care utilization by LGBTQ individuals [68, 82–84]. Perceived discrimination from health care providers and denial of health care altogether are common experiences among LGBTQ patients and have been identified as contributing factors to health disparities [85–88]. Disparities in health care access and outcomes experienced by LGBTQ patients are compounded by vulnerabilities linked to racial identity [89–91] and geographic location [92]. Biases among health care providers toward LGBTQ patients are common [93, 94] despite commitments to patient care equality. These biases, also known as negative stereotypes, may be either explicit or implicit [95]. A large study of heterosexual, first-year medical students demonstrated that about half of students reported having negative attitudes toward lesbian and gay people (i.e., explicit bias) and over 80% exhibited more negative evaluations of lesbian and gay people compared to heterosexual people that were outside of their conscious awareness (i.e., implicit bias) [93]. Research in social-cognitive psychology on intergroup processes defines explicit biases as attitudes and beliefs that are consciously accessible and controlled; they are typically assessed via self-report measures and are limited by an individual's awareness of their attitudes, motivation to reveal these attitudes, and ability to accurately report these attitudes [96, 97]. In contrast, the term "implicit bias" refers to attitudes and beliefs that are unconscious (i.e., outside of conscious awareness) and automatic [98, 99]. Health care provider biases are correlated with poorer access to services, quality of care, and health outcomes [95, 100–102]. Explicit biases held by

health professionals toward racial/ethnic minorities, women, and older adults are known to affect clinical assessments, medical treatment, and quality of care [103]. Importantly, implicit bias measures are more strongly associated with real-world behaviors than explicit bias measures [104] and are linked to intergroup discrimination [105]. Health care providers' implicit biases toward vulnerable patient groups may persist despite an absence of negative explicit attitudes [106], resulting in preconceived notions about patient adherence, poor doctor-patient communication, and micro-aggressions, all of which can interfere with optimal care. With less time and limited information processing capacity, providers' decisions are increasingly governed by stereotypes and implicit biases [107, 108]. Medical student and provider biases may contribute to health disparities in vulnerable populations by negatively impacting communication with patients and decisions about patient care [97, 99]. Taken together, these findings suggest that medical students and healthcare providers are likely to underestimate or to be unaware of their implicit biases toward LGBTQ patients, particularly when they are rushed or fatigued, which could impact their behavior and judgments in ways that contribute to health disparities experienced by LGBTQ populations. Theoretical models of bias reduction note that implicit biases are "learned over time through repeated personal experiences and cultural socialization" and are "highly resistant to change" [95, 97]. According to the prejudice habit-breaking framework, overcoming the "habit" of implicit bias "requires learning about the contexts that activate the bias and how to replace the biased responses with responses that reflect one's nonprejudiced goals" [109]. Long-term reductions in implicit racial bias have been achieved through an intervention promoting bias awareness (i.e., feedback following the IAT) and brief training in bias reduction strategies (i.e., stereotype replacement, counter-stereotypic imaging, individuation, perspective-taking, increasing opportunities for intergroup contact) [109].

29.4.2 LGBTQ-Related Bias Reduction Programs

A meta-analysis of LGBTQ-related bias reduction programs conducted with primarily undergraduate students found large, positive program effects on knowledge and moderate effects on explicit biases toward LGBTQ individuals. Programs providing education, promoting contact with LGBTQ individuals, and/or combining education and intergroup contact had the best results; a major limitation was that few studies included implicit bias measures [110, 111]. Another promising study found a medium effect for a program utilizing biographical vignettes of LGBTQ exemplars in reducing implicit bias (assessed with the Sexuality IAT) toward LGBTQ persons [110, 112]. Together, these studies demonstrated that biases, including those targeting LGBTQ individuals, could be modified [113]. One critical gap in the literature is whether training programs incorporated into medical education can help students become more aware of potential implicit biases toward LGBTQ patients and develop effective bias reduction skills to combat these biases in medical school, residency, and beyond [10]. To date, research testing the effectiveness of implicit bias reduction strategies among medical students and physician providers has primarily focused on vulnerable racial and ethnic groups [114]. When Morris et al. performed a systematic review to determine the effectiveness of programs to reduce health care student or provider bias toward these LGBTQ patients, they identified 639 abstracts addressing bias among medical, nursing, and dental students or providers; from these abstracts, 60 articles were identified as medical education programs to reduce bias; of these articles, 13 described programs to reduce bias toward LGBTQ patients [10]. Bias-focused educational interventions were effective at increasing knowledge of LGBTQ health care issues and experiential learning interventions were also effective at increasing comfort levels working with LGBTQ patients [10]. Intergroup contact was effective at promot-

ing more tolerant attitudes toward LGBTQ patients [10]. Despite promising support for bias education in increasing knowledge and comfort levels among medical, nursing, and dental students or providers towards LGBTQ persons, it was difficult to identify any interventions that assessed changes in implicit bias among students or providers [10]. Maybe it could be possible in the future.

29.5 SGME for Postgraduate Course and Medical Students in Seoul National University College of Medicine

The term "SGME" is very unfamiliar in the medical field in South Korea. The author's group experimented with two kinds of SGME. One was offered as an elective for second-year medical students at the Seoul National University College of Medicine and received positive reviews from 2017 to 2021. Four professors in the division of Cardiology, Hepatology, Gastroenterology, and Clinical Pharmacology participated at this education. In the year of 2021, among the 160 second-year medical students, 22 (13.75%) chose this subject and the education was performed by Zoom. All of the medical students showed curiosity for the SGME and tried to learn the approach of sex/gender-specific medicine.

A second course was offered to graduate students in translational medicine in 2017 and 2019. This course employed the text *Sex and Gender Aspects in Clinical Medicine* [2]. This foundational text reported finding for sex/gender in circulatory, respiratory, digestive, kidney, and autoimmune diseases, as well as endocrinology, hematology, neurology, and clinical pharmacology [2, 11]. In 2019, three subjects regarding "Sociocultural approach to gender" and "Considering sex in basic research using Cells" were added according to students' recommendation [11] (Table 29.1). In 2017, faculties and students who took the course were unfamiliar with sex/gender-specific medicine before attending the classes, but by the end of the semester, they were motivated to apply sex/gender-specific analysis to their clinical research [11]. In 2017, ten professors and 12 students (10 medical doctors, one nurse, and one's major was public heath) participated in this class and completed the survey [11]. Participants were satisfied with this class for sex/gender-specific medicine concepts, which had never been experienced before [11]. Five-question surveys revealed that both students and professors improved their awareness about sex/gender differences in medicine ($p = 0.026$) and "gendered innovation" ($p < 0.001$) after class [11] (Fig. 29.1). Sex/gender-specific medicine was regarded as fundamental for precision medicine or researches and 85.3% agreed that sex/

Table 29.1 Curriculum in a graduate course on sex/gender-specific medicine in the graduate school of translational medicine in a Seoul National University College of Medicine-based medical school (adapted from Park et al. [11])

	Week	Contents
Lecture plan	1st	Introduction to gendered innovations in biomedicine and public health and necessity of sex/gender-specific medicine
	2nd	Gendered innovations in science
	3rd	Understanding about sex hormone and the effects of hormone replacement therapy
	4th	Sex/gender differences in hepatology
	5th	Sex/gender differences in psychiatry
	6th	Sex/gender differences in gastrointestinal diseases
	7th	Sex/gender differences in pulmonary diseases
	8th	Sociocultural approach to gender
	9th	Sex/gender differences in autoimmune diseases
	10th	Sex/gender disparities in obesity
	11th	Sex/gender differences in cardiovascular disease
	12th	Considering sex in basic research using cells
	13th	Sex/gender differences in pharmacokinetics and pharmacodynamics
	14th	Sex/gender differences in pancreatobiliary diseases
	15th	Class evaluation

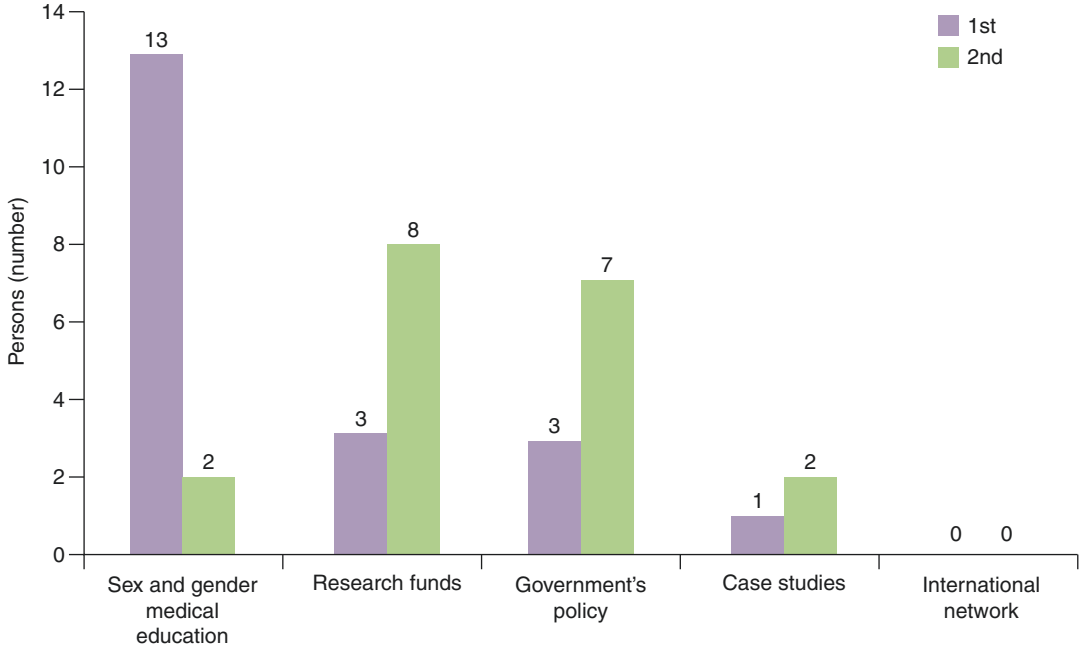

Fig. 29.1 Participant responses to what is the most important factor for establishing gender-based medicine in biomedicine and research (first and second choices) (adapted from Park et al. [11])

gender-specific medicine should be integrated into routine medical curricula [11]. Most of them chose medical education and research funds as the most important requirements to settle down sex/gender-specific medicine in the biomedical fields [11]. This experience was published as an article entitled "Experiences with a graduate course on sex/gender medicine in Korea" [11], which received considerable attention from the world.

29.6 Conclusions

Recent studies have documented significant differences between women and men in the incidence, symptoms, morbidity, and mortality of various diseases, highlighting the importance of sex/gender-specific medicine. Thus, it is important to understand that sex/gender-specific medicine is not women's health, which focuses primarily on women's reproductive health. Rather sex/gender-specific medicine analyses differences between men and women throughout the entire body and recognizes that understanding these differences will improve the precision and quality of health care for both women and men. Developing a sex/gender-specific medicine curriculum in the gastroenterology is necessary and it is a challenging task. Assessing institutional resources and collaborating between disciplines can anchor this undertaking [9]. These efforts will strengthen medical students and fellowship education and can serve as a backbone for the academic and clinical advancement of GI health [9]. Another necessary education program is regarding LGBTQ individuals because they experience higher rates of health disparities. These disparities may be driven, in part, by biases of medical providers encountered in health care settings [10]. Systemic review showed that bias-focused educational interventions were effective at increasing knowledge of LGBTQ health care issues and experimental learning interventions were also effective at increasing comfort levels working with LGBTQ patients [10]. In South Korea, the author's group experimented with two kinds of SGME for

undergraduate medical students and graduate students from 2017 up to now. These courses improved students' and professors' awareness about sex/gender-specific medicine and "gendered innovation."

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30 Work-Life Balance of Korean Gastroenterologists Depending on Sex and Age

Nayoung Kim

30.1 Introduction

Physician's life is a demanding and stressful field in the world. Occupational stress can adversely affect the quality of care, decrease job satisfaction, and potentially increase medical errors. The notion that a physician benefits others rather than themselves has long been respected, particularly in the East [1]. For this reason, physicians have been thought to be devoted to patients, giving priority to them over everything else [1]. Therefore, work style reform and the work–life balance of doctors, especially among clinicians, young doctors, and women doctors, are considered the last untouched islands for work style reform among various occupations [1]. Recently physician burnout is increasingly recognized as a systemic health care problem [2]. Prior research has identified the adverse impact on physician health and patient care [3]. Recently, studies have begun to examine the impact on health care delivery [4]. Gastroenterologists are prone to many health-related risks with their job because they have various roles, including as an endoscopist, a physician, and an academic professional [5]. Because gastroenterologists perform repetitive diagnostic and therapeutic procedures with unstable posture, musculoskeletal pain frequently occurs [6–8]. In addition to the physical problems, the psychosocial job stress from the clinical responsibility for patient outcomes, interaction with various people, and the demand to complete administrative and research work on time [9, 10] can lead to other health problems for doctors, such as cardiovascular [11], gastrointestinal [12] and psychiatric diseases [10, 12]. The consequences of physician's burnout are negative effects on patient care, professionalism, physicians' own care and safety, and the viability of health-care systems. As there are sex and age differences of physicians, it is important to analyse the physician's low career satisfaction and burnout depending on sex and age. However, the work-life balance and sex differences have not been fully studied among gastroenterologists, not only in Eastern countries including Korea but also in Western countries including the United States. In this chapter, the physician's burnout including gastroenterologists, especially in the young women doctors, is briefly reviewed.

30.2 Physician Burnout

Recently, the work-life conflicts and burnout of doctors have been reported as important problems worldwide [3, 13–15]. Among 6880 US physicians, the satisfaction rate with their jobs

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was only 40.9%, and less satisfaction was related to a higher burnout rate (overall 54.4%) [3]. In the study, after adjusting for age, sex, and working hours, physicians showed 48% less satisfaction for their work-life balance (OR 0.68; 95% CI, 0.62–0.75) and a higher risk (approximately 2 times higher) for burnout (OR 1.97; 95% CI, 1.80–2.16) [3]. In China, the work-family conflict also decreased job satisfaction [16], and it was positively related to emotional exhaustion and cynicism, which is a major component of burnout [14]. As the work-life conflict and subsequent burnout did directly affect the physician's underperformance and medical errors [17], it is a crucial and urgent issue for the entire health-care system [5]. In this section, the author would like to review the published articles regarding physician burnout [7, 18].

30.2.1 Surgeon Burnout

A surgeon is a medical doctor with the trained specialty to operate in need of variety of surgical procedure. Surgery involves the core treatment of most of diseases such as cancer, acute care, trauma, reconstructive medicine and even transplantation. Therefore, the importance of a surgeons' role cannot be emphasized enough in our health care service. In other countries, surgery is one of the most popular specialties as a meaningful and rewarding job for medical doctors. However, in Korea, a surgeon became a job that most doctors want to avoid as their life-time specialty. There are numerous reasons that can be considered as factors related to this trend in Korea such as low insurance costs for surgical procedures, an increased workload for the individual surgeon due to the shortage of workforce, risk of medical sue and others. One of the main reasons is the high workload and occupational stress of Korean surgeons [19]. The work in an operating room can be stressful, hectic and physically demanding. Surgery is sometimes an emergency event, performed in a high pressure, life-or-death situation. Surgeons typically work long hours and may also take emergency calls. In addition, they may need to work when they are sleep-deprived and often work under stress [20].

30.2.1.1 Surgeons

Kang et al. [21] have conducted an electronic survey of 621 Korean surgeons for the occupational stress [21]. Sixty-five questions were used to assess practical and personal characteristics and occupational stress using the Korean occupational stress scale (KOSS). The mean KOSS score was 49.31, which was higher than the average of Korean occupational stress (45.86) or that of other specialized professions (46.03) [21]. 16.6% showed high emotional exhaustion, and 28.5% had a high score of depersonalization. Overall, 197 surgeons (31.7%) were considered to suffer from burnout and these surgeons had a much higher KOSS score (55.34 ± 9.69) than those surgeons without burnout (46 ± 8.77, $p < 0.001$) [21]. Young age, female gender, long working hours, and frequent night duties were significantly related to the higher KOSS score. Having spouse, having hobby and regular exercise decreased the KOSS score. Multiple linear regression analysis showed that long working hours and regular exercise were the independent factors associated with the KOSS score. Less than 50% of surgeons answered that they would become a surgeon again [21]. Most surgeons (82.5%) did not want to recommend their child follow their career suggesting that Korean surgeons have high occupational stress and low level of career satisfaction [21].

30.2.1.2 Surgical Residents

A number of studies have reported the high level of stress and reduced job satisfaction of residents [18, 22–24]. These days, surgical residents have a heavier workload and experience more stress due to the labour force shortage, which has been caused in part by a decrease in the rate of applicants and an increased workload in systematized hospitals [25]. Moreover, the dropout rate for surgical residents during training is also increasing in South Korea. This overworking of surgical residents leads to a vicious cycle, with the application rate for surgical residency continuously decreasing year by year. The decrease in the number of applicants and the high dropout rate of surgical residents have become serious social issues in South Korea. Many things may cause these problems, but one

of the important reasons is the excessive workload and high occupational stress these surgical residents are put under [19]. The application rate for surgical residents in Korea has continuously decreased over the past few years. The demanding workload and the occupational stress of surgical training are likely causes of this problem. Kang et al. [18] performed a study to investigate occupational stress and its related factors in South Korean surgical residents. With the support of the Korean Surgical Society, they conducted an electronic survey of Korean surgical residents related to occupational stress. They also used the Korean Occupational Stress Scale (KOSS) to measure occupational stress [18]. The mean KOSS score of the surgical residents was 55.39, which was significantly higher than that of practising surgeons (48.16, $p < 0.001$) and the average score of specialized professionals (46.03, $p < 0.001$) [18] (Table 30.1). In terms of lifestyle characteristics, regular exercise was significantly associated with lower KOSS score ($p = 0.001$) in univariate analysis but the significance disappeared in multivariate analysis. In multiple linear regression analysis, the mean number of assigned patients, resident occupation rate and exercise were all significantly associated with KOSS score [18].

Table 30.1 Burnout of surgical residents in comparison to specialized professionals (adapted from Kang et al. [18])

Question	Surgical residents	Practising surgeons	*p*-value[a]
Burnout			0.002
Yes	66 (66.7)	131 (25.1)	
No	33 (33.3)	391 (74.9)	
Would become a physician again?			0.002
Yes	50 (50.5)	348 (66.7)	
No	49 (49.5)	174 (33.3)	
Would become a surgeon again?			0.519
Yes	46 (46.5)	261 (50.0)	
No	53 (53.5)	261 (50.0)	
Would you recommend this career to your child?			0.493
Yes	15 (15.2)	94 (18.0)	
No	84 (84.9)	428 (82.0)	

Values are presented as number (%)
[a]Chi-square test

30.3 Women Physician

It has been over 180 years since Elizabeth Blackwell became the first woman to obtain a medical degree in the United States, paving the way for other women to enter the field [26]. Today, women account for 35.4% of all physicians and 17.6% of gastroenterologists [27]. In other countries, women comprise more than 20–40% of the current medical practising field including Korea [28]. Furthermore, the number of women entering medical school is increasing. However, there remains a dearth of women in leadership positions in national societies and in the highest rungs of academia [26]. For example, in 2015 women constituted <20% of gastrointestinal fellowship program directors and <10% of section/division chiefs [29, 30]. While there has been some positive change with a recent increase in women in executive leadership of GI societies (American Gastroenterological Association [AGA], American Association for the Study of Liver Disease [AASLD], American College of Gastroenterology [ACG] and the American Society for Gastrointestinal Endoscopy [ASGE]), this has not translated into leadership [26]. This could be related with severe work-life conflict in women doctors compared to men [31–33].

30.3.1 Work-Life Conflict of Women Gastroenterologists

Women doctors are exposed to more demanding situations for their household management than men doctors [31, 34]. Although it depends on culture and customs in each country, in general, the situation is worse in Japan and Korea [1, 5]. Even among US surgeons, women were more responsible for childcare, meal planning and grocery shopping significantly in both trainees and faculties [31]. In particular, physician mothers in procedural specialties demonstrated low career satisfaction because of their high domestic responsibilities [35]. Because of the work-family conflict, women tended to leave the academic position and forgo promotion opportunities [14,

28]. Women with academic jobs had difficulty being fully dedicated to their professor jobs [36] and were less likely to have major authorships in high-impact medical journals [37]. Moreover, women doctors are still underrepresented in medical conferences as speakers [28].

A recent article from Lerchenmueller et al. [38] showed that women researchers do not promote their work with the same degree of 'positivity' (i.e., using words like 'novel', 'unique', and 'unprecedented' to describe their research) as their men counterparts. This pattern, the authors suggest, reflects a lack of self-promotion that leads to less prominence in research authorship [26]. Indeed, given the importance of publications and authorship in the promotion process, the above research is a cause for concern, suggesting that a more structured approach should be used to address the myriad issues involved [26]. Indeed, some overt barriers that may exist include a lack of appropriate mentorship and/or sponsors combined with competing outside obligations and the need for work–life balance—all factors that may impact advancement [26]. That said, more insidious forces may be at play: Women are more likely to experience a phenomenon known as 'impostor syndrome'—a feeling that they are successful 'by accident' or through hard work but not due to inherent qualification and intelligence [39]. As a result, women are less likely to promote themselves and often (mistakenly) believe that others will recognize the quality of their work [40].

30.3.2 Authorship of Women Gastroenterologists and Trends in the Proportion of Women Speakers at Medical Conferences in the United States and in Canada, 2007 to 2017

Speaker invitation and selection at conferences represent important opportunities to influence gender equity within medicine, and authorship is also a very meaningful indicator of academic leadership. Recently there were interesting reports regarding the authorship of women gastroenterologists [41] and trends in the proportion of women speakers at medical conferences in the United States and in Canada, 2007 to 2017 [28]. Actually authorship, speaker invitation and selection at conferences represent important opportunities to influence gender equity within medicine [28].

30.3.2.1 Authorship of Women Gastroenterologists

In order to demonstrate that an 'authorship gender gap' of national society publications, Bushyhead and Strate [41] retrospectively evaluated 90 technical reviews and guidelines between 2007 and 2019 from ACG and AGA. They determined the ratio of women authors to the total number of authors [41]. They also evaluated trends in these ratios over three periods of time. Among the 90 examined publications, only 21% had women authorship [41]. When looking at temporal trends, they found that although the number of published technical reviews and guidelines increased over time, women authorship remained consistently below that of men. In terms of society-specific trends, the authors discovered that women authorship did increase from 21 to 35% in AASLD publications from 2007–2010 to 2015–2019; women authorship in ACG publications remained stable and actually declined among published AGA guidelines [41] (Fig. 30.1). Lastly, only 18% of first authors were women in all of the examined publications [41]. To explain these disparities, the authors pointed out that women still represent a minority of practising gastroenterologists in the United States, though this does not explain the overall increase in women authorship of original research over a similar period of time [26]. Though there is no obvious explanation for the ongoing disparity between men and women in the authorship of society reviews and guidelines, the authors of this study speculate there may be an implicit bias toward males as experts or leaders [26]. Similar trends exist across other medical specialties and may have broader implications for the promotion of women to senior positions, and the visibility of women in their respective fields [26].

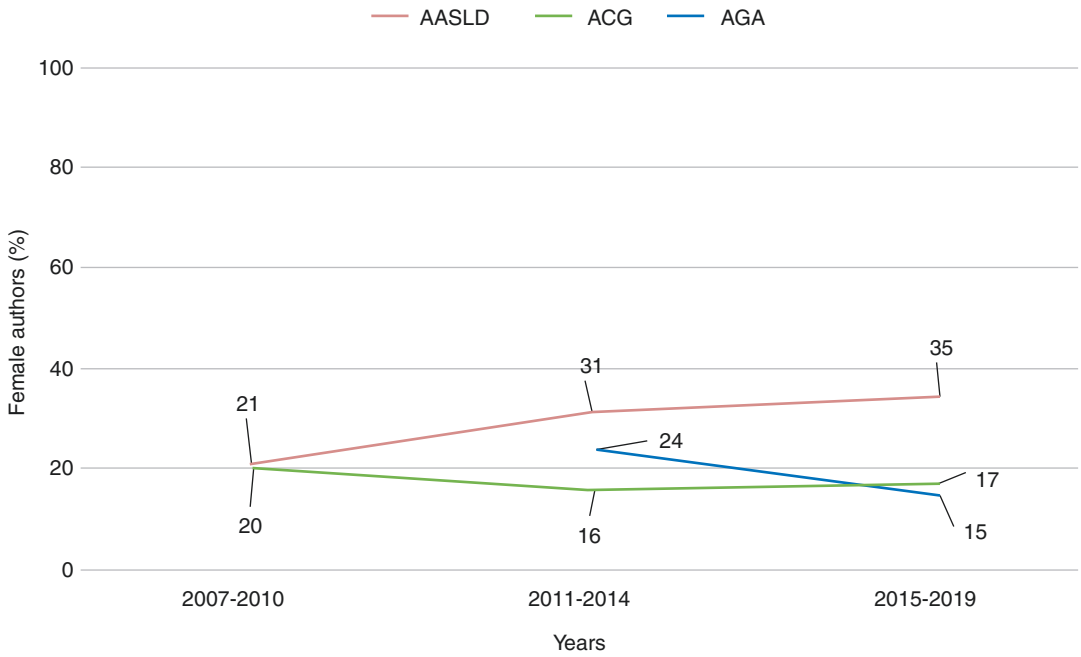

Fig. 30.1 Proportion of female authors of guidelines and technical reviews. *AASLD* American Association for the Study of Liver Disease, *ACG* American College of Gastroenterology, *AGA* American Gastroenterological Association (adapted from Bushyhead and Strate [41])

30.3.2.2 Trends in the Proportion of Women Speakers at Medical Conferences in the United States and in Canada, 2007 to 2017

Ruzycki et al. [28] analysed the trend during the last decade in the proportion of speakers who were women at major academic medical conferences held in Canada and in the United States. The mean (SD) proportion of female conference speakers for all meetings significantly increased from 24.6% for 40 meetings in 2007 to 34.1% for 181 meetings in 2017 ($p < 0.001$) [28]. The mean proportion of women speakers at medical specialty conferences was 9.8% higher (Standard Error [SE], 1.9%; $p < 0.001$) than the mean proportion of female speakers at surgical specialty conferences for all years analysed [28]. The mean proportion of women speakers at conferences was similar to the mean proportion of active women physicians across all specialties in the United States and in Canada for all years analysed [28]. Although these findings indicate that the proportion of women speakers at medical conferences increased during the last decade, the authors suggest that women continue to be underrepresented.

30.3.2.3 Solutions to Improve the Women Leadership

How could it be fixed? The solution is complex, requiring a combination of education and awareness to address these deep and subtle issues. Nevertheless, there also has to be a more structured and conscious attempt to actively include expert women in the creation of high-impact guidelines [26]. To overcome the existing status quo, women gastroenterologists need to empower themselves and one another to rise to prominent positions in research and society governorship [26]. Academic institutions and national societies also need to set the example by supporting and, more importantly, promoting women. As things continue to move in a positive direction and more women occupy leadership positions in gastroenterology, at some point the term ‘women leaders’ will be replaced by simply by the term ‘leaders’ [26].

30.4 Work-Life Conflict and Its Health Effects on Korean Gastroenterologists According to Age and Sex

Gastroenterologists perform various roles, including as an endoscopist, a physician and an academic professional [5]. In addition, gastroenterologists perform repetitive diagnostic and therapeutic procedures with unstable posture; musculoskeletal pain frequently occurs [6–8]. Furthermore, the psychosocial job stress from the clinical responsibility for patient outcomes after therapeutic endoscopy, interaction with various people including nurses during endoscopic procedure, and the demand to complete administrative and research work on time [9, 10] can lead to other health problems such as cardiovascular [11], gastrointestinal [12] and psychiatric diseases [10, 12]. As there are sex and age differences of gastroenterologists, it is important to analyse the physician's low career satisfaction and burnout depending on sex and age. However, the work-life balance and sex differences have not been fully studied among gastroenterologists. The author performed study entitled 'Work-life conflict and its health effects' with grant from Korea Federation of Women Science and Technology Association, and Korean Medical Women's Association. Total 222 [124 men (55.9%) and 98 women doctors (44.1%)] participated in an anonymised self-responded electronic questionnaire survey about their daily activities and symptoms for 14 days [5]. Musculoskeletal, gastrointestinal and mental symptoms were scored using a numerical scale. The Maslach Burnout Inventory was used to measure the burnout score [5].

30.4.1 Work-Life Hours of Korean Gastroenterologists

The mean time spent at work and home among Korean gastroenterologists was 71.5 ± 19.0 (54.0 ± 16.1 for intrahospital work and 17.5 ± 9.5 h per week for extrahospital work) and 16.6 ± 15.9 h per week, respectively [5] (Fig. 30.2a). Although there was no significant between the sex differences in working time (Fig. 30.2b), the amount of time spent at home was significantly higher among women (20.7 ± 19.0 vs. 14.3 ± 13.3 h/week; $p = 0.007$), and it was noted in all age groups (Fig. 30.2c). Moreover, time dedicated to 'others' tended to be shorter for women than for men (78.1 ± 22.6 vs. 80.9 ± 23.2 h/week; $p = 0.421$, Fig. 30.2a). The work-life ratio did not significantly differ between the sexes (men, 0.86 ± 0.49 vs. women, 0.77 ± 0.39; $p = 0.226$) [5] (Fig. 30.3).

30.4.2 Musculoskeletal, Gastrointestinal, and Mental Symptoms

For musculoskeletal symptoms, 89.6% of participants suffered from any grade of pain, and it was significantly more frequent for women (Fig. 30.4a). For all age groups, women showed a significantly higher total pain score than men (6.1 ± 4.9 vs. 3.6 ± 3.9; $p < 0.001$) [5]. The difference in pain scores between the sexes was particularly significant among participants in their 30s (6.1 ± 5.1 vs. 3.5 ± 3.9; $p < 0.001$; Fig. 30.4a) [5]. According to regression analyses, sex ($\beta = 2.55$, 95% CI, 1.40–3.69, $p < 0.0001$), the number of colonoscopies ($\beta = 0.06$, 95% CI, 0.02–0.11, $p = 0.008$) (Fig. 30.4b) and work-life ratio ($\beta = 2.63$, 95% CI, 1.37–3.88; $p < 0.001$) were independently related to the musculoskeletal pain score after adjusting for age group [5].

For gastrointestinal symptoms, 53.6% responded that they had suffered from any grade of symptoms (Fig. 30.4c). The prevalence was not significantly different between the sexes; however, it did increase with age ($p = 0.040$). In detail, epigastric pain, dyspepsia, nonspecific abdominal pain and stool calibre change were found in 29 (16.7%), 31 (17.3%), 17 (9.1%) and 30 (16.9%) respondents, respectively [5]. Functional gastrointestinal disease, as confirmed by the Rome IV criteria, was found in 55 (24.8%) participants. As shown in Fig. 30.4c, men in their

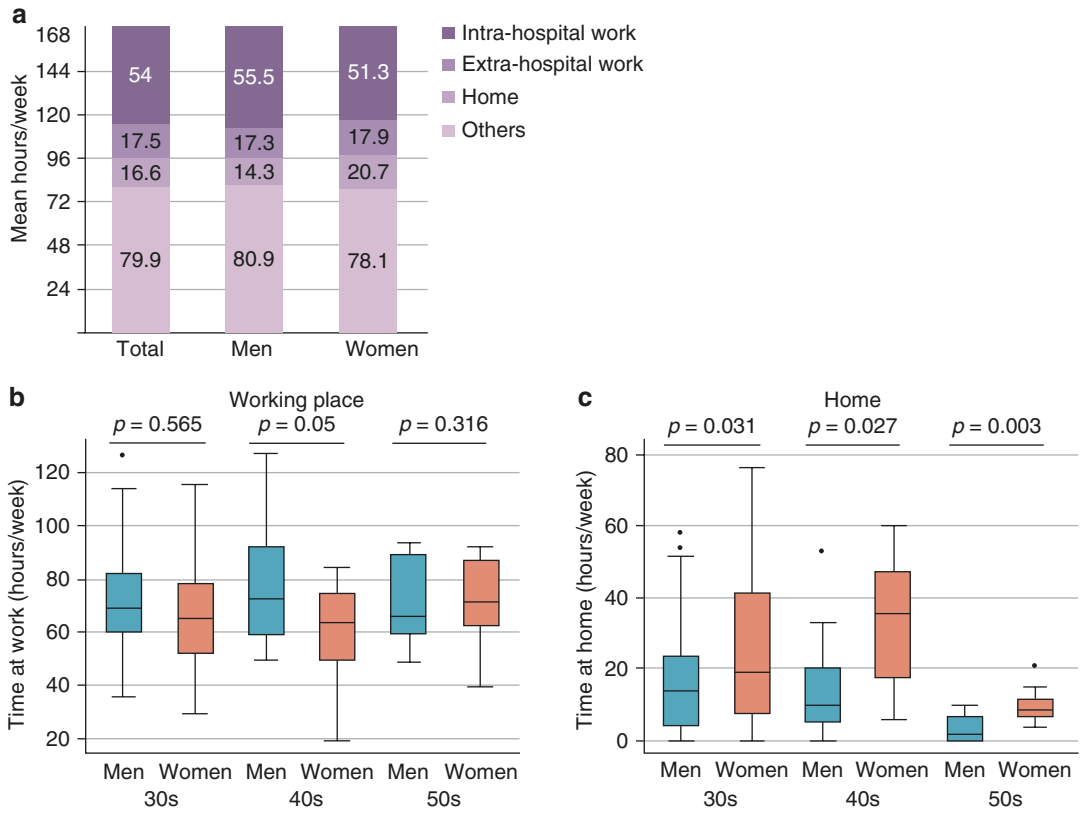

Fig. 30.2 Work and life hours of Korean gastroenterologists, according to sex (**a**) and age groups at working place (**b**) and at home (**c**) (adapted from Jang et al. [5])

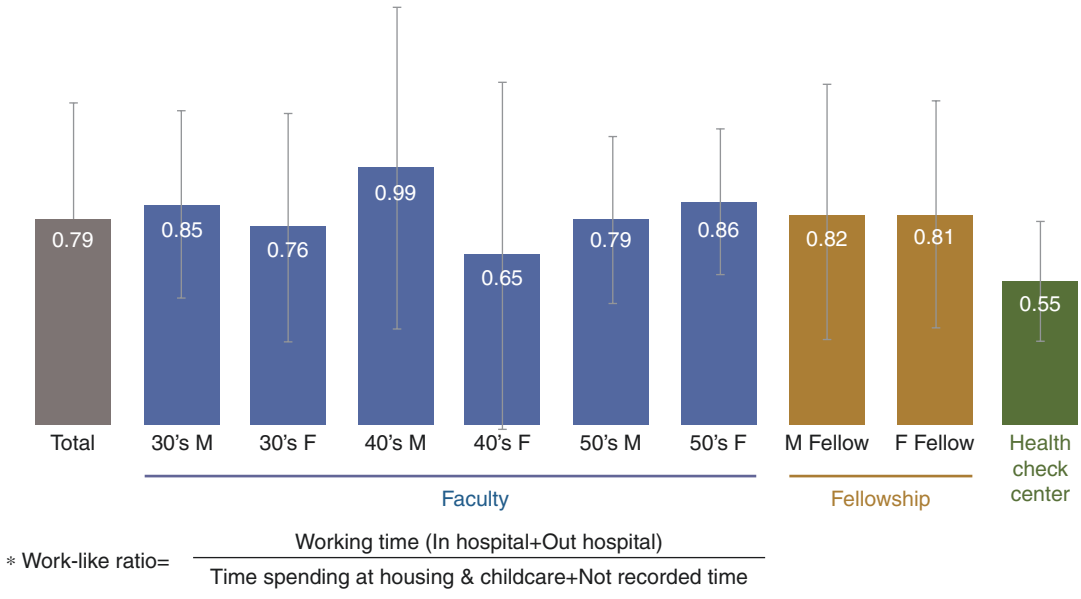

Fig. 30.3 The work-life ratio depending on age and sex (adapted from Jang et al. [5])

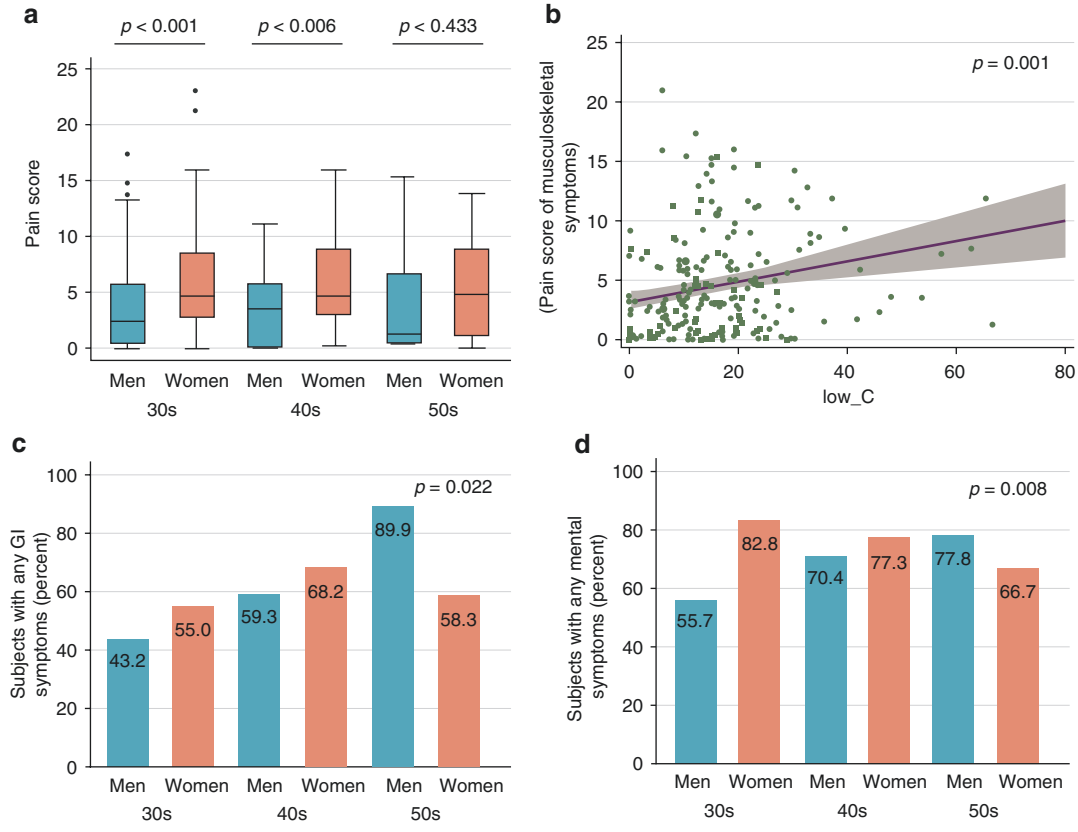

Fig. 30.4 Musculoskeletal, gastrointestinal and mental symptoms depending on age and sex. (**a**) Musculoskeletal pain score, (**b**) the correlation between the number of colonoscopy and musculoskeletal pain, (**c**) gastrointestinal symptoms and (**d**) mental symptoms (adapted from Jang et al. [5])

Table 30.2 Independent factors affecting the presence of severe mental symptoms in Korean gastroenterologists (adapted from Jang et al. [5])

	OR	95% CI	*p*-value
Age	1.3	0.71–2.40	0.392
Women vs. men	1.4	0.57–3.28	0.476
Severe musculoskeletal pain	8.2	3.33–20.39	<0.001
Number of procedures >60/weeks	2.5	1.06–6.03	0.037
Work/life ratio	3.1	1.31–7.18	0.010

50s showed the highest prevalence of 88.9% ($p = 0.022$), followed by women in their 40s (75.0%) and 30s (64.6%) [5].

Notably, mental symptoms such as anxiety and depression were highly prevalent in this study population. A total of 153 (68.9%) participants responded that they had any degree of mental problems, which was reported significantly more often by women than men (79.6% vs. 60.5%, $p = 0.002$) (Fig. 30.4d). In each age and sex group, women in their 30s showed the highest prevalence of any mental symptoms (87.5%, $p = 0.008$); however, all other groups also demonstrated high results (Fig. 30.4d). More severely, the HADS score was in the abnormal range (score 11–21) for 74 (33.3%) doctors [5]. The multivariable analysis showed that severe mental symptoms affecting normal life were independently affected by severe musculoskeletal pain, a high number of endoscopic procedures and a high work-life ratio (Table 30.2) [5].

The work-life ratio was related to all symptoms that we asked about. As the work-life ratio increased, pain (β = 2.27, 95% CI, 0.96–3.58; $p < 0.001$), gastrointestinal symptom (β = 071, 95% CI, 0.01–1.41; $p = 0.048$) and mental symptom (β = 1.88, 95% CI, 0.64–3.11; $p = 0.003$) scores also increased [5].

30.4.3 Burnout and Its Related Factors

With the Maslach Burnout Inventory survey, 143/222 (64.4%) of the respondents met the criteria for burnout. By domain, a high emotional exhaustion score (≥27), high depersonalization score (≥10) and low personal accomplishment (≤33) were found in 118 (53.2%), 108 (48.7%) and 116 (52.3%) of the respondents, respectively [5].

The mean emotional exhaustion, depersonalization and personal accomplishment scores of the study population were 26.8 ± 11.6, 9.9 ± 5.9 and 30.9 ± 8.6, respectively. Among 6 age and sex groups, the emotional exhaustion score was highest among women in their 30s (29.0 ± 10.2) and 40s (28.0 ± 11.8), despite being statistically insignificant ($p = 0.419$) (Fig. 30.5a), and women in their 30s had the worst scores in the depersonalization (11.6 ± 5.5, $p = 0.012$) (Fig. 30.5b) and personal accomplishment (28.3 ± 8.5, $p = 0.003$) domains (Fig. 30.5c). As the work-life ratio increased, the personal accomplishment score also significantly increased (β = 3.06, 95% CI,

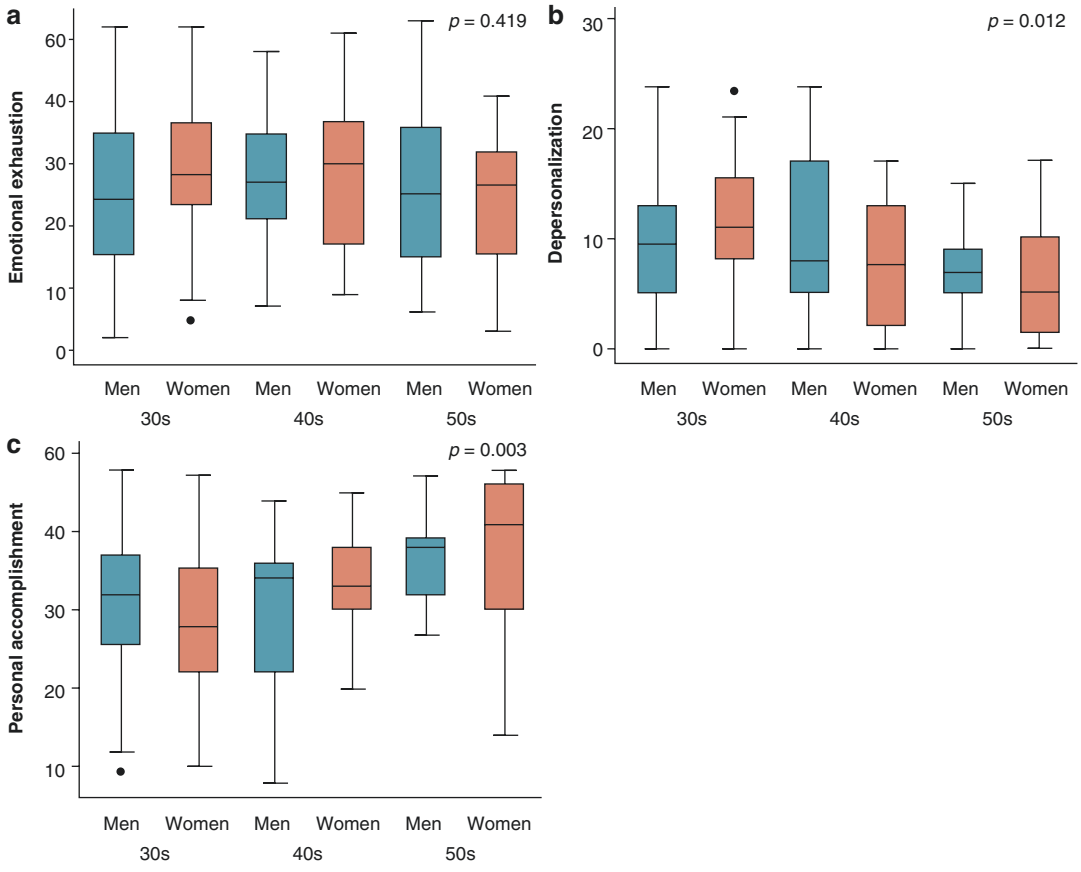

Fig. 30.5 Maslach Burnout Inventory scores according to age and sex among Korean gastroenterologists for emotional exhaustion (**a**) depersonalization (**b**) and personal accomplishment (**c**) domains (adapted from Jang et al. [5])

0.54–5.59, p = 0.018); however, the emotional exhaustion score decreased with borderline significance (β = 2.92, 95% CI, 0.51–6.35, p = 0.095) [5].

30.4.4 Job Satisfaction

The mean job satisfaction score was 3.71 ± 0.97 of 5 points, and it tended to be lower among women (3.58 ± 1.02) than in men (3.82 ± 0.92, p = 0.067) (Fig. 30.6a). According to age and sex groups, the job satisfaction score was lowest among women in their 40s (p = 0.049) compared with the other groups (3.72 ± 0.96 among men in their 30s, 3.53 ± 0.93 among women in their 30s, 3.96 ± 0.81 among men in their 40s, 3.45 ± 1.18 among women in their 40s, 4.33 ± 0.71 among men in their 50s, and 4.08 ± 1.16 among women in their 50s). The job satisfaction score was significantly correlated with the emotional exhaustion (β = −0.03, 95% CI, −0.04 – −0.02, p < 0.0001), depersonalization (β = −0.05, 95% CI, −0.07 – −0.03, p < 0.0001) and personal accomplishment scores (β = −0.04, 95% CI, 0.03–0.06, p < 0.0001), but not with the work-life ratio (β = 0.03, 95% CI, −0.26–0.32, p = 0.852) [5]. 14% of the participants responded that they were not satisfied with their jobs (Fig. 30.6a). Particularly, fewer women doctors answered that they would reselect the profession of doctor (Fig. 30.6b) and even gastroenterologist (Fig. 30.6c) if they had a chance to select their job again compared to men [5].

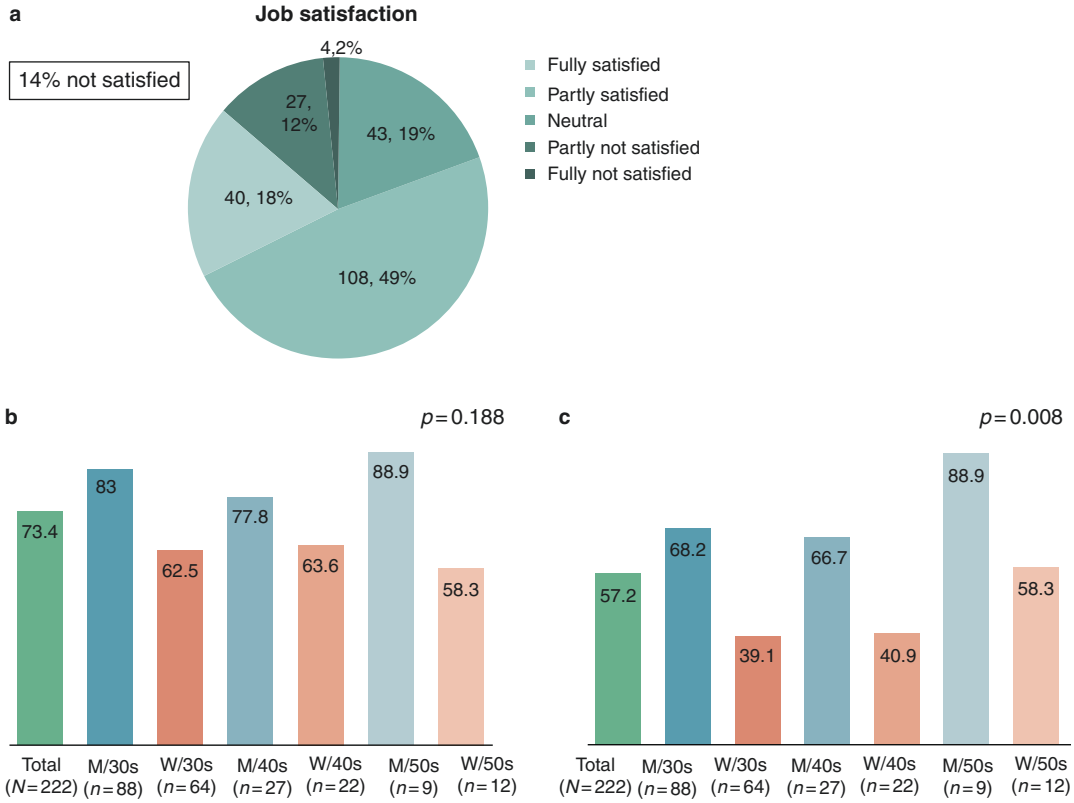

Fig. 30.6 Job satisfaction and reselection job among Korean gastroenterologists. Job satisfaction (**a**), possible reselection rate of the profession of doctor (**b**), and even gastroenterologist (**c**) if they had a chance to select their job again (adapted from Jang et al. [5])

30.5 Interventions to Prevent and Reduce Physician Burnout

The literature indicates that both individual-focused and structural or organisational strategies can result in clinically meaningful reductions in burnout among physicians [42]. However, further research is needed to establish which interventions are most effective in specific populations, as well as how individual and organizational solutions might be combined to deliver even greater improvements in physician wellbeing than those achieved with individual solutions. In addition, there was a report that professional self-concept functioned to protect medical school faculty from burnout [43]. Furthermore, the professional self-concept subscale, which included satisfaction and communication skill, was found to significantly affect burnout [43]. This may be a strategy that fortifies the professional identity of medical school faculty, and it is suggested that educational programs that are directed toward this goal be established [43].

30.5.1 Systemic Review and Meta-Analysis Regarding Intervention Study for the Physician's Burnout

To prevent and reduce burnout, West et al. [42] performed systemic review regarding intervention study for the physician's burnout. They identified 2617 articles, of which 15 randomised trials including 716 physicians and 37 cohort studies including 2914 physicians met inclusion criteria [42]. Overall burnout decreased from 54% to 44% (difference 10% [95% CI, 5–14]; $p < 0.001$; I^2 = 15%; 14 studies) (Fig. 30.7), emotional exhaustion score decreased from 23.82 points to 21.17 points (2.65 points [1.67–3.64]; $p < 0.001$; I^2 = 82%; 40 studies), and depersonalization score decreased from 9.05 to 8.41 (0.64 points [0.15–1.14]; $p = 0.01$; $I^2 = 58\%$; 36 studies) [42]. High emotional exhaustion decreased from 38% to 24% (14% [11–18]; $p < 0.001$; $I^2 = 0\%$; 21 studies) and high depersonalization decreased from 38% to 34% (4% [0–8]; $p = 0.04$; $I^2 = 0\%$; 16 studies).

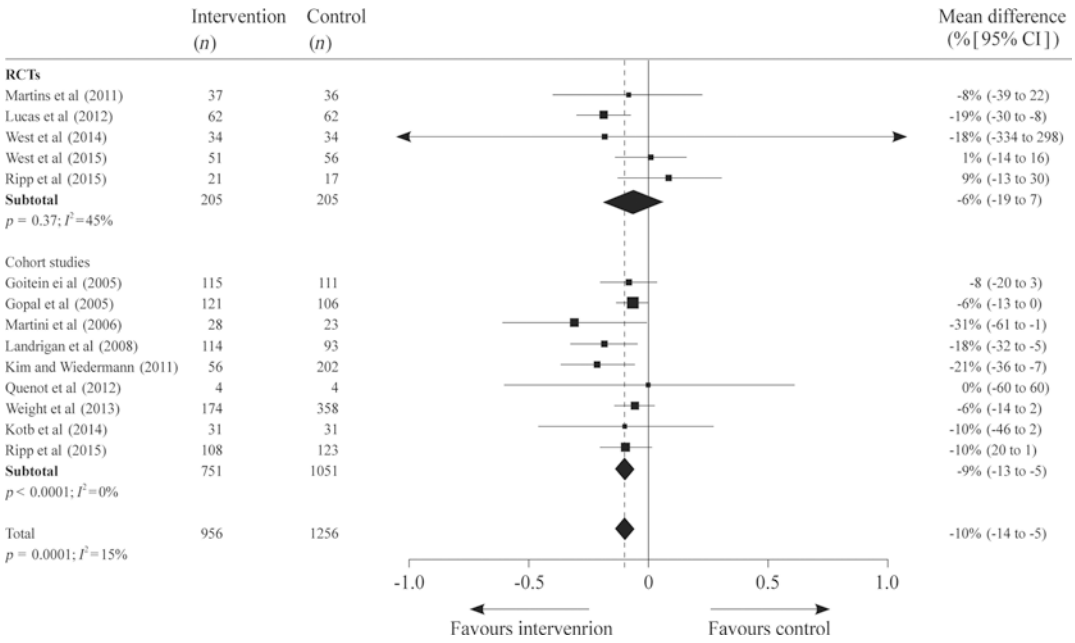

Fig. 30.7 Overall burnout. For the five randomized controlled trials and nine cohort studies reporting differences in overall burnout, the pooled mean difference estimate was a significant absolute reduction from 54% to 44% (difference 10% [95% CI, 5–14]; $p < 0.001$; $I^2 = 15\%$) (adapted from West et al. [42])

30.5.2 The Effect of a Team-Based, Incentivized Exercise Program Among Physician Trainees

Weight et al. evaluated the effects of an incentivized exercise program on physical activity (PA), quality of life (QoL) and burnout among residents and fellows (RFs) in a large academic medical centre [44]. In January 2011, all RFs at Mayo Clinic in Rochester, Minnesota (N¼1060), were invited to participate in an elective, team-based, 12-week, incentivized exercise program [44]. Of the 628 RFs who completed the baseline survey (59%), only 194 (31%) met the US Department of Health and Human Services recommendations for PA [44]. Median reported QoL was 70 on a scale of 1 to 100, and 182 (29%) reported at least weekly burnout symptoms [44]. A total of 245 individuals (23%) enrolled in the exercise program [44]. At study completion, program participants were more likely than nonparticipants to meet the Department of Health and Human Services recommendations for exercise (48% vs. 23%; $p < 0.001$) [44]. QoL was higher in program participants than in nonparticipants (median, 75 vs. 68; $p < 0.001$) [44]. Burnout was lower in participants than in nonparticipants, although the difference was not statistically significant (24% vs. 29%; $p = 0.17$) [44]. These results suggest that a team-based, incentivized exercise program is effective for the intervention for the physician's burnout.

30.5.3 Intervention for the Japanese Women Gastroenterologists

The Japanese Society of Gastroenterology (JSGE) has established a women gastroenterologists' association and has recently developed a career support committee in the name of supporting not only women doctors, but also young doctors, including interns and residents [1]. The career support committee has been planning hands-on training to support female and young doctors in academic societies, increasing the number of women councillors, and developing childcare facilities at national and domestic academic meetings. Recently, the career support committee held a nationwide case study competition symposium at the annual meeting of JSGE in order to support young doctors regardless of gender and recruit young gastroenterologists to the society; it was received with great popularity by many of the participants [1]. This activated discussions among young doctors, and the younger generation was successfully brought back to the JSGE meeting. The 2nd Career Support Committee/Branch Women's Doctor Meeting in 2019 will be held on Saturday, November 23, 2019, during JDDW2019 in Kobe, Japan. The agenda at this time is a report on the activities of women's gastroenterology associations in each regional branch of JSGE and discussions regarding the career support committee's plans for the 106th general meeting to be held in April 2020. Yet, the committee was not directly involved in issues such as the current working conditions of doctors, working hours, overtime, and childcare leave. Nonetheless, the Ministry of Health, Labor, and Welfare in Japan has currently started the process of reforming doctors' working environment, slated to be completed in 2024 [1]. They plan to implement continuous working hour regulations and inter-work interval regulations from the viewpoint of ensuring the health and medical safety of hospital doctors. Besides, they are investigating the use of objective indicators to identify doctors who are unable to secure sufficient sleep time in order to ensure their continued health. The Japanese government has begun to develop regulations for the working environments of doctors [1].

30.6 Conclusions

Recently, the work-life conflicts and burnout of doctors have been reported as important problems worldwide. In addition, physician burnout such as overall burnout, emotional exhaustion score and depersonalisation score has reached epidemic levels in both of physicians in training and practising physicians. The burnout is rather serious not only for surgeons but also for the gastroenterologists. Furthermore, the burden of

young woman doctors are the most serious group in this pandemic state of COVID-19. The consequences are negative effects on patient care, professionalism, physicians' own care and safety, and the viability of health-care systems. In the survey for the total of 222 Korean gastroenterologists (124 men and 98 women) from 44 nationwide centres in South Korea Korean women spent more time performing housework and parenting (20.7 ± 19.0) compared to men (14.3 ± 13.3, $p = 0.007$). Musculoskeletal pain was found in 199 respondents (89.6%), and women had a higher total pain score compared to men in all age groups ($p = 0.016$). Gastrointestinal and mental symptoms were found in 119 (53.6%) and 153 (68.9%), respectively. Work-life ratio was significantly correlated with musculoskeletal ($p < 0.001$), gastrointestinal ($p = 0.048$) and mental symptoms ($p = 0.003$). Using the Maslach Burnout Inventory, 64.4% of the respondents demonstrated burnout. Moreover, emotional exhaustion, depersonalization and personal accomplishment scores were worst in women in their 30s or 40s. These show that work-life imbalance and burnout were most severe in young women doctors due to their domestic demands among physician's burnout. Systemic review showed that intervention could decrease overall burnout from 54% to 44% (difference 10% [95% CI, 5–14]) suggesting that both individual-focused and structural or organisational strategies can contribute to improve the burnout among physicians.

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