Chapter

The Interaction between the Gut Microbiota and Chronic Diseases

Temitope Sanusi-Olubowale

Abstract

The world is experiencing an increase in chronic diseases like diabetes, inflammatory bowel diseases, cancer, cardiovascular diseases, obesity, and diabetes preceding disease like gestational diabetes. Most of these diseases can be prevented and mitigated if individuals pay attention to the causative factors. One of such factors is the type of microorganisms in an individual's gut. Even though there are innate beneficial microorganisms in the human gut, pathogenic microorganisms can invade the gut, changing the inborn population of the gut microbiota. The changes in the gut microbiota population have been linked to several diseases. This chapter, therefore, describes gut microbiota and their interaction with specific diseases. Also discussed in this chapter are the changes to gut microbiota composition that pose a risk to the host. There is substantial evidence that diseases are initiated or worsened with a change in the gut microbiota composition. Therefore, the gut microbiota plays a crucial role in individuals' health and requires human efforts to keep them in the right population. Furthermore, making lifestyle changes, particularly food choices and behaviors such as the misuse of medications and excessive alcohol consumption, should be monitored and controlled to support gut health.

Keywords: Gut microbiota, Bacteria phylum, Gestational diabetes, Chronic diseases, Gut dysbiosis

1. Introduction

Chronic diseases (CD) are unfavorable health statuses lasting for over one year or more [1, 2]. Such diseases require continual medical attention and activities that could mitigate the severity [1, 2]. The diseases are the leading cause of death and incapacity worldwide, with influences on all socio-economic setups. In 2002, the CD was reported as the cause of 60% of death and 43% global distress [1, 3]. In 2020, the cause of death through CD had risen to 73% and universal distress of 60%, as shown in **Figure 1** [3]. The cause of some of these diseases was attributed to different factors such as genes, poor diet, and lifestyle [1, 4]. The common CD includes diabetes, cancer, cardiovascular diseases, chronic pulmonary diseases, obesity, arthritis, stroke, Alzheimer's diseases, chronic kidney diseases, inflammatory bowel diseases, tooth decay, and epilepsy [1, 3, 5]. Some diseases are signals to the potential development of chronic diseases. Women who have gestational diabetes are at risk of developing type 2 diabetes, hypertension, cardiovascular diseases, and obesity, just as high blood cholesterol could be indicative of future coronary heart diseases, obesity, and hypertension [6, 7].

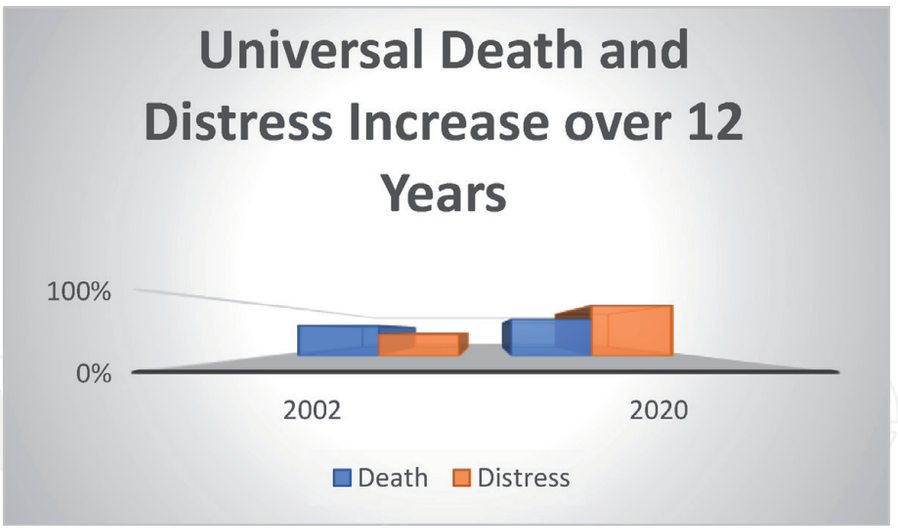

Figure 1.
Chart showing the rate of increase in death and distress as caused by chronic diseases.

Asides from death and health difficulties associated with CD, there are several negative impacts socially and economically. The family of people suffering from one or more CD reported increased personal life burden, financial difficulties, impaired social relations, and intrinsic rewards [8, 9]. Likewise, treating CD and helping people with such diseases significantly impact different countries' finances. It has become a substantial financial burden to nations [10, 11]. In the United States of America, $327 billion is spent annually on medical costs for diabetes [5]. About $147 billion per year for the health cost of obesity, $164 billion for arthritis, $500 billion for Alzheimer's diseases, epilepsy takes $8.6 billion annually, and $45 billion is spent on annual health care for tooth decay [5]. In 2015, a forecasted percentage of Gross Domestic Product (GDP) loss was reported for different countries worldwide. Brazil was expected to lose 3.21% of GDP, Canada, 0.64%, China, 3.94%, India, 5.05%, Nigeria, 3.07%, Russia, 12.35%, Tanzania, 4.19%, United Kingdom, 5.18% GDP losses from death caused by diseases. In another report, the United States loses $1.1trillion annually from the lack of productivity of citizens living with CD. Reducing the rate of obesity alone in the country would increase productivity by $254 billion and $60 billion in reductions in treatment costs [10, 11].

With the national, family, and personal losses associated with CD, methods of curbing the rising rate call for more research, government and non-governmental initiatives, and policies [10]. One research aspect was to figure out the genesis of all these diseases [4, 12]. From different findings, diverse components contribute to the incidence of diseases or increase the risks of developing these diseases. For example, the cause of some of these diseases was attributed to individual genes, other influences such as unhealthy diet, overweight, sedentary lifestyle (lack of physical activities), and risk behaviors such as tobacco use and excessive alcohol were identified. One crucial discovery on factors contributing to disease incidence was the gut microbiota [13–15].

2. The gut microbiota

The human body consists of several microorganisms which were innately beneficial to the host. These colonies of microorganisms that have settled in the human's gastrointestinal tract (GIT, gut) over many years include bacteria, eukaryotes, bacteriophages, archaea, and fungi, and they are called the gut microbiota (GM) [13, 16]. The GM has evolved and established a commensal relationship with the human host

over many years. Hence, they are equally referred to as commensals microorganisms because they provide health benefits to the host while the commensals get nutrients from the host without harming the host [13, 16].

There are trillions of microorganisms colonizing humans, but research focuses on the bacteria community [17, 18]. Some years ago, scientists reported that the bacteria cells in the GIT are numerous, much more than the number of cells in the body. Some other researchers claimed that the bacterial cells in the GIT are ten times more than body cells [13, 19]. Recent studies, however, showed human cells and bacterial cells are at a ratio of 1:1 [13, 19, 20].

Humans' GM is developed from birth [19, 21, 22]. Particularly for babies delivered vaginally, the microbiota in the mother's cervix is passed on to the babies. This GM received from birth builds the first wall of defense in children, and the population of GM gradually changes as the child grows. In addition, gut bacteria aid adaptive immunity, a crucial function of the GM in the human's body [13, 21, 22].

2.1 Functions of gut microbiota

The GM proffer benefits to the host. The first known function is to assist in building immunity after birth. The GM has other functions in the body; they contribute advantages anatomically, physiologically, and immunologically [19, 23].

2.1.1 Anatomical and physiological functions

The GM is known for the breakdown of carbohydrates, particularly the indigestible dietary fibers, like cellulose, resistant starch, pectin, oat, wheat bran, and inulin [24, 25]. The absorption of nutrients from dietary fiber has been associated with satiety feeling after eating, thus preventing overeating. The GM metabolizes protein by the secretion of digestive enzymes. Synthesis of vitamin K and B vitamins such as vitamin B12, riboflavin, niacin, and folate, and other digestive enzymes are also performed by GM [23, 24]. The GM also performs physiological benefits of strengthening the gut, shaping the intestinal epithelium, and harvesting energy [13].

Anatomically, the GM assists in maintaining the mucosal barrier's strength by shaping the intestinal epithelium, thereby sustaining gut integrity. Furthermore, the metabolites produced during the breakdown of dietary fibers are absorbed by the epithelial cells to assist cell proliferation, differentiation, and apoptosis of harmful cells, like the cancer cells [23, 26]. The GM is sometimes called the second brain because of its effect on the brain. This is because the metabolites released during the breakdown of fibers are absorbed to support brain activities [19, 27].

2.1.2 Immunological functions

The GM provides immunity to the host by building colonization resistance, a situation in which the innate GM antagonizes foreign microorganisms' colonization and prompts the preservation of structural and functional protective mucosal barriers [14, 15]. The GM in humans also invades and takeover foreign pathogens in the gut [19, 21]. The metabolites produced by GM, the short-chain fatty acids (SCFAs), reduces the intestinal pH, thus making survival difficult for foreign microorganisms [14, 15]. The functions of SCFAs will be discussed in subsequent sections of this chapter. In addition, the GM improves the integrity of intestinal mucosal to prevent invasion by foreign organisms. Another function of GM is the metabolism of xenobiotics [14, 15]. Xenobiotics, which are foreign materials to the bodies' biology, include drugs or chemicals that could be toxic [15]. Thus, the GM prevents the body from toxins by breaking them down from their harmful state.

2.2 The pathogenicity of the gut microbiota

Even though gut bacteria are beneficial, they could become pathogenic in their interaction with changes in the host environment and vectors. For example, if microorganisms giving benefits to the host invades other sites they do not usually colonize, that change in their environment could result in them acting as pathogens which could cause diseases [28, 29]. Furthermore, microorganisms in the body can also contribute to polymicrobial infections. Polymicrobial infection occurs when different microorganisms in the body interact and cooperate to create diseases in the host [28, 29]. Therefore, treatment has to be offered to take care of all microorganisms contributing to the infection.

One salient way the GM becomes harmful to the body is if its population in the gut undergoes unusual changes due to drug use, aging, sicknesses, lifestyle, and unhealthy food choices. This abnormal change in the population can result in gut dysbiosis (GD), which would be discussed in the subsequent section. In addition, changes to GM populations have been related to autoimmune situations, allergies, and chronic diseases. The incidence of diseases like autism, asthma, colitis, obesity, gestational diabetes, type 1 & 2 diabetes has been linked to GM's activity in its natural state or an altered nature [19]. Studies have equally shown a disparity in the types of GM or their populations present in a healthy and sick adult. For example, the type and population of GM in people living with gestational diabetes and type 2 diabetes differs from individuals free from the disease [24, 30]. The composition and population of the GM are identified to be influenced by factors such as diet, feeding type, birth delivery mode, and age of hosts [30, 31].

3. Phylum of gut bacteria in human body

Researchers identified the prominent type of GM colonizing the human gut, which is bacteria; therefore, subsequent sections of this chapter will focus on gut bacteria. Recently, scientists compiled data that shows there are about 2172 species of microorganisms isolated from humans. These species were classified into 12 phyla. The predominant phyla that make up about 93.5% of humans' colonies are bacteria, Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes [13, 28]. Out of these four predominant phyla, 31·1% are phylum Firmicutes, particularly families Bacillaceae, 15.7%, and Clostridiaceae, 11·4% [28]. Proteobacteria occupies 29.5% of GM species isolated in humans, with 20% belonging to the family Enterobacteriaceae. Phylum Actinobacteria constitutes 25·9% of the GM isolated in humans, with 24·2% identifies as family Mycobacteriaceae. Bacteroidetes amount to 7·1% of the total species cultured from humans, and 29% of the phylum belongs to the family Prevotellaceae [15]. About 386 of the isolated species were identified to be anaerobic. Such microbiota would be found in the oral cavity and GIT – the mucosal regions [13].

3.1 Proteobacteria

Proteobacteria (PBAC) was initially called purple bacteria because of their reddish pigmentation, **Figure 2**. In 1988, a group of scientists studied the purple bacteria and their relatives. The scientists discovered that most of the bacteria and their relatives were neither purple nor photosynthetic. However, the bacteria group had great biological significance through physiological features. Therefore, scientists named these groups of microorganisms PBAC [31, 33, 34]. Characteristics of PBAC are:

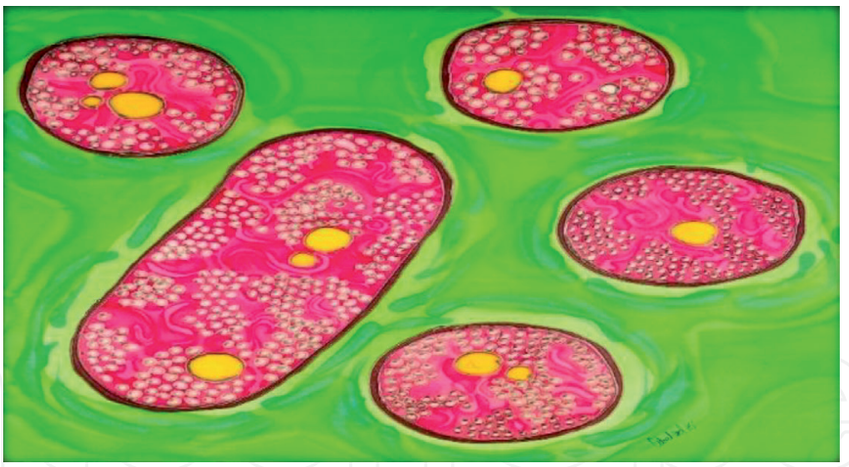

Figure 2.
Proteobacteria are called purple bacteria because of reddish pigmentation [32].

- The PBAC is gram-negative bacteria with an outer membrane made up of lipopolysaccharides. This outer membrane makes them resistant to drugs, particularly antibiotics [34, 35].

- The PBAC classes, families, and genera differ in motion and metabolic activities. They have different shapes. Some have flagella, some are non-motile, while some perform bacteria gliding [34, 35].

- The PBAC is facultative or obligatory anaerobic. They can be chemoautotrophs or heterotrophic, and they are pathogens [34, 35].

- Some classes and genera are of considerable importance to medical experts, food industries, and scientists within this phylum. Class Gammaproteobacteria includes important pathogens, *Salmonella*, *Vibrio*, *Pseudomonas*, *Escherichia*, *and Yersinia*. Genera such as *Helicobacter* and *Campylobacter* from class Epsilonproteobacteria are common in the GIT [34].

- Proteobacteria are allied to inflammation; therefore, their population increases in the gut in a condition prone to inflammation [31, 36].

3.2 Actinobacteria

Actinobacteria (ABAC), another populous bacteria in the human gut, are gram-negative bacteria and are mainly aerobic, even though some can survive under anaerobic conditions [37, 38]. The ABAC has other characteristics;

- The DNA of ABAC contains a high level of Guanine and Cytosine [37].

- Even though there are several genera, the pathogens that live in humans include Mycobacterium, Corynebacterium, Nocardia, and some species of Streptomyces [37, 38].

- The ABAC are secondary producers of metabolites; therefore, they are of interest for pharmacological and commercial purposes. The subclass Actinobacteridae and the order Actinomycetales are particularly of medical and economic benefit because their metabolites have antibiotics, particularly the genus Streptomyces [37, 38] (**Figure 3**).

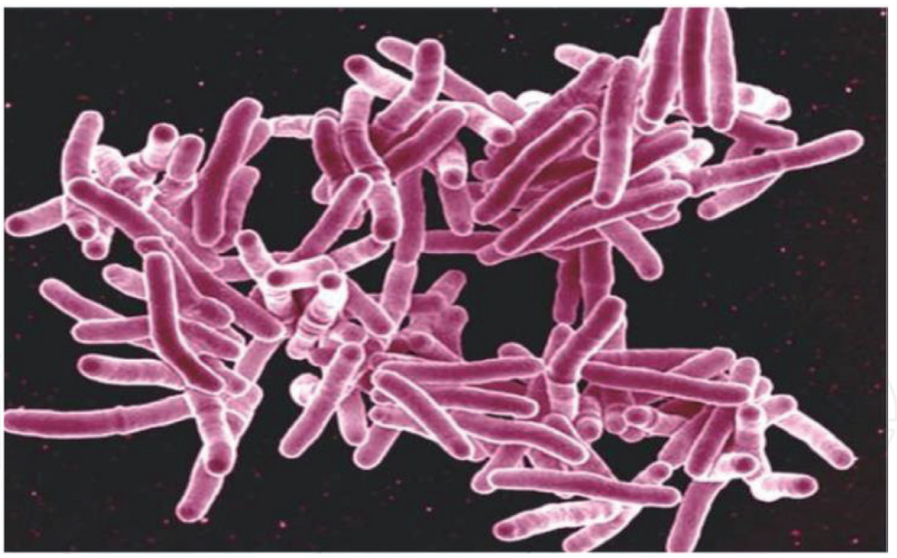

Figure 3.
Mycobacterium tuberculosis*, one of the species of Actinobacteria hosted by humans [39].*

3.3 Firmicutes

Firmicutes are gram-positive bacteria, though some have a pseudo outer membrane that makes them stain gram-negative [35, 40]. Phylum Firmicutes is notable for microorganisms that profer health benefits. Some genera of Firmicutes are administered as probiotics to profer gut health benefits. Characteristics include;

Firmicutes could be round (cocci) or rod-like (bacillus) in shape. Unlike the ABAC, they have a low level of Guanine and Cytosine in their DNA; they are acid-tolerant and take part in metabolic and physiological activities [35, 40].

There are two major classes; the anaerobic Clostridia and the obligate or facultative aerobic Bacilli [35, 40]. These are notable pathogens and beneficial microorganisms within this phylum. One crucial order of this phylum is the Lactobacillales (Lactic Acid Bacteria). Lactic acid bacteria produce lactic acid as a metabolite during glucose fermentation. Lactic Acid Bacteria appear everywhere in the food and are therefore regarded safe for consumption. In addition, they are known to contribute health benefits to the human gut [35, 40].

The genera for Lactic Acid Bacteria include *Lactococcus*, *Enterococcus*, and *Streptococcus*. The genus *Lactobacillus* (**Figure 4**) is the most common microbe used as probiotics [35, 40]. Firmicutes are either anaerobic, particularly *Clostridia*, while class Bacilli is an obligate or facultative aerobe. Therefore, bacteria belonging to class Bacilli would not grow or populate in an anaerobic environment [35, 40].

3.4 Bacteroidetes

Bacteroidetes are gram-negative, non-spore-forming, and anaerobic bacteria [42]. Bacteroidetes can survive in several environments, including the gut and skin. The class Bacteroidia is the most studied class of this phylum GM [42]. One common genus in this class is the *Bacteroides*. *Bacteroides* are clinically significant and have a mutualistic relationship with the host [42, 43]. The mutualistic behavior of *Bacteroides* occurs if they are retained in the gut. Once *Bacteroides* escape their familiar environment, they become pathogenic and can cause

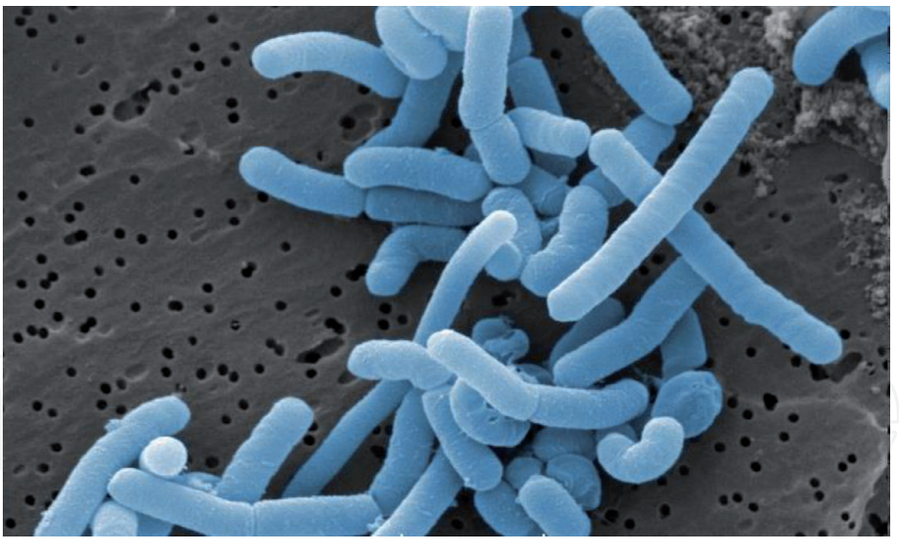

Figure 4.
Lactobacillus paracasei *[41].*

diseases such as an abscess in different parts of the body [43]. Other features of *Bacteroides* include:

- *Bacteroides* break down large molecules in the human guts into simpler molecules, while the bacteria derive their energy source from their host. The bacteria hence help to produce beneficial fatty acids [42, 43].

- *Bacteroides* prevent other pathogens from colonizing and infecting the gut of the host [42].

- *Bacteroides* have species that are highly resistant to many antibiotics [43]

4. Short-chain fatty acid producing bacteria

The GM is a balanced environment of different microorganisms such as bacteria, viruses, bacteriophages, archaea, and fungi; however, the bacteria community preserves the homeostasis of the gut. The bacteria community contains some groups of gut bacteria that produce SCFAs mentioned in Section 2.1.2. These fatty acids include acetate, propionate, and butyrate. The SCFAs are an essential fuel for the intestinal epithelial cells, and they assist the gut barrier functions and sustain homeostasis in the intestine [23, 44].

These groups of gut bacteria ferment indigestible dietary fibers to produce SCFAs. Dietary fibers such as resistant starch, inulin, wheat, oat bran, cellulose, pectin, and Guam gum are suitable substrates for bacteria activities and fermentation. Out of all prominent bacteria phylum identified in the human body, the Firmicutes and Bacteroidetes are more of the SCFAs producers [23, 44]. The acetate and propionate are produced by phylum Bacteroidetes, while the Firmicutes produce more of the butyrate [23, 45]. Another genus, such as *Bifidobacterium*, from phylum Actinobacteria and some Proteobacteria, could also produce butyrate. It is also important to note that some butyrate producers like Bacteroides are anaerobic bacteria and would not be active in aerobic situations; however, class Bacilli of Firmicutes would thrive because they are aerobes [23, 35, 46]. The aerobic environment in a human gut will suppress the growth of some butyrate-producing bacteria but allow the growth of aerobic pathogens like *Salmonella typhimurium* [23].

4.1 Functions of short-chain fatty acids in the gastrointestinal tract

1. The SCFAs control the gene expression for energy metabolism. Butyrate, in particular, is the primary energy source for colon cells. Therefore, SCFAs are involved in the energy metabolism of colon epithelial cells [23, 47, 48].

2. Propionate act as gluconeogenesis substrate in the intestine, where it can be oxidized to glucose. Acetate is also available in the tissues, where it can be transformed to butyrate and oxidized by muscles or used for lipogenesis [27, 49].

3. The SCFAs regulate the development of organoids. Hence, a cell proliferating attribute. The SCFA can induce mucus-secreting cells to secrete mucus that protects the mucosa [23, 48].

4. The SCFAs have been identified to suppress cancer cells or causing apoptosis to cancer cells. In addition, they perform the antimicrobial function because they can disrupt the osmotic and pH balance, creating an environment not accommodative to other microorganisms [48].

5. The SCFAs promote epithelial barrier function by initiating genes responsible for tight junctions and reforming protein, increasing epithelial resistance to pathogen invasion [23, 48].

6. The SCFAs induce prostaglandins which have an anti-inflammatory effect, thus reducing the pro-inflammatory effect. In addition, it induces anti-inflammatory cytokines to reduce the inflammation of the gut, which has been attributed to the cause of the host's susceptibility to some diseases [23, 49].

5. Interactions of gut microflora and diseases

The colonization of GM starts from childbirth; however, the composition starts changing based on different factors. For example, the birth delivery method, the mode of feeding, and the type of food offered to an infant determine GM's population [14, 22, 50]. For example, researchers reported that the type of bacteria composition in children fed with breast milk differs from children fed with the formula [14, 22]. In the same way, children born via natural birth have different GM compositions from children born via assisted delivery, such as caesarian surgery [14, 22]. As infants are introduced to solid food, GM composition makes another change [14, 22]. It is also important to note that the composition of GM also differs based on the part of GIT. For instance, the types of GM in the colon are different from the types in the stomach. This difference is because of factors such as the redox condition of the different organs. Other factors are the pH of the organ environment, allergies, the motility of organs, secretions in each organ such as the gastric acid secretion of the stomach, and the undamaged ileocaecal valve [14, 22]. Bacteria colonizing the guts from birth are also referred to as commensal bacteria because they benefit the host [14, 51]. For instance, Bacteroidetes and Firmicutes are the major phyla involved in breaking down macromolecules into simpler forms, particularly the indigestible fibers. However, abnormal changes can occur to the GM, leading to an abnormal composition of bacteria. This condition can be the onset of chronic diseases such as type 1 and 2 diabetes, obesity, cardiovascular diseases, cancer, and inflammatory bowel diseases [14, 52].

Surprisingly, abnormal bacteria composition has been linked with diseases that are considered temporary due to physiological changes like metabolic and immunological changes [7, 53]. An example is a gestational diabetes. During pregnancy, some women who cannot produce enough insulin develop gestational diabetes. The physiological changes occurring during pregnancy, such as weight gain, reduce the effective use of insulin, resulting in insulin resistance, as shown in **Figure 5**. The development of insulin resistance makes the body of the pregnant woman demands more insulin production. Even though gestational diabetes occurs late in pregnancy, some women experience insulin resistance before pregnancy [53, 55]. Women with gestational diabetes, if not well managed, might have their unborn babies at risk of being over 9lbs weight birth, which could bring delivery hazards to the mother. Also, the baby might be born earlier than anticipated, which could cause health problems for the baby. In addition, the baby might be born with low blood sugar. Women who have gestational diabetes are equally at a 40% risk of developing type 2 diabetes. About 5 to 20% of all world pregnancies are affected by gestational diabetes, and the percentage is increasing [7, 53, 56]. These statistics suggest a possible increase in people at risk of developing or living with type 2 diabetes, one of the world's major chronic diseases. Changes in the GM population are noticed in people who have gestational diabetes and chronic diseases. This change in population is the gut dysbiosis.

5.1 Gut dysbiosis

Gut dysbiosis is a condition in which there is a change in the balance of GM composition. Some phyla become highly populated while some reduce in population. This condition creates abnormality in the human GIT, and the pathogenesis of commensals bacteria starts [52]. Most bacteria in the gut are beneficial; however, when the balance in population changes in these bacteria gut colonies, as shown in **Figure 6**, dysbiosis occurs [7, 52]. Some symptoms of dysbiosis are mild and temporary; however, leaving dysbiosis untreated could result in severe symptoms associated with chronic diseases [52]. Even though commensals bacteria antagonize invading microorganisms, sometimes foreign microorganisms can seize the epithelium and overthrow the commensals, destabilizing the immune response [52]. After that, the invading pathogens induce inflammation to which they would be resistant, facilitating their growth and changing the balance of commensals bacteria. Viruses create series of mechanisms that regulate the activities of the

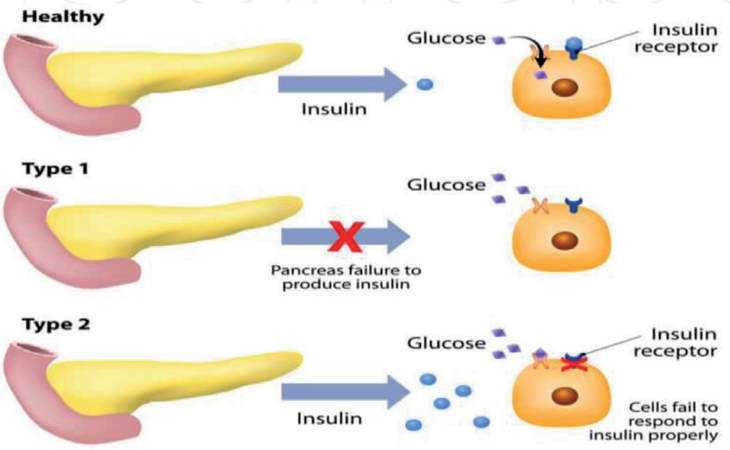

Figure 5.
Insulin resistance during gestational diabetes [54].

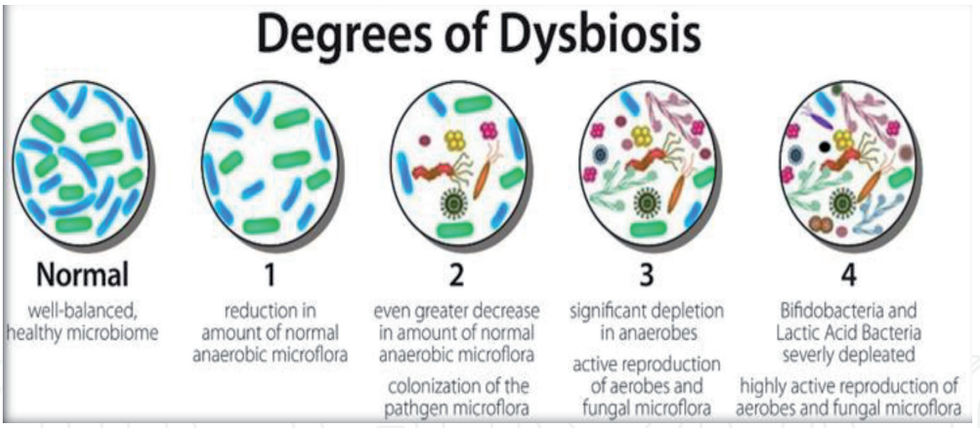

Figure 6.
Gut dysbiosis [57].

commensals, making them harmful to the host [16, 58]. Factors causing dysbiosis include a dietary change, chemical consumption like insecticides, alcoholism, improper use of medications, particularly antibiotics, poor dental hygiene, unprotected sex, stress, and anxiety, psychological stress. All these factors could change the balance of GM. In addition, the genotype and immune metabolic functions can alter the population of commensal microbes [52, 59, 60].

Symptoms of dysbiosis are dependent on the location of GM imbalance development and the types of bacteria involved. Symptoms could be gas, bloating, diarrhea, constipation, and cramps [52, 61]. To determine the imbalance of GM, most researchers make use of a human stool [52, 62]. The collected sample is then tested to determine the type of bacteria in the host's body. The organic acid test is another test used medically to determine imbalance [52, 62]. Some bacteria produce organic acids as metabolites. Therefore, the concentration of the organic acid in the urine sample determines the host's bacteria population. The hydrogen breath test is another test conducted to determine dysbiosis. In this case, gases from the mouth are tested for imbalance [52, 62]. Unfortunately, diseases tolerance varies in people; not everyone with dysbiosis shows severe symptoms that call for urgent attention or medical checkup, particularly at a young age. Ignoring or leaving the dysbiosis untreated, however, can result in many severe diseases.

5.2 Diseases associated with dysbiosis

The GM is partly responsible for the physiology of the body systems. Changes in the balance or population of GM have been linked to bowel diseases, allergies, and chronic metabolic diseases such as diabetes, obesity, cardiovascular diseases, and short-term disease like gestational diabetes.

5.2.1 Type 1 diabetes

According to research, Firmicutes such as *Lactobacillus*, Actinobacteria such as *Bifidobacterium* decreased in populations in children diagnosed with type 1 diabetes. In contrast, the population of Firmicutes such as *Clostridium* and *Veillonella*, Bacteroidetes like *Bacteroides* and *Prevotella* increased [14, 15]. Patients with Type 1 diabetes had low butyrate-producing and mucin degrading microbes, while pathogenic bacteria increased in population in the gut. Butyrate-producing bacteria and mucin degrading microbes are good for gut health [14, 63]. The functions of SCFAs, of which butyrate is one, are discussed

in Section 4.1. Mucin degradation releases complex carbohydrates and produces SCFAs like acetate and propionate [64].

5.2.2 Type 2 diabetes

In patients with type 2 diabetes, Clostridia and Bacilli Firmicutes decreased in population while PBAC increased. Butyrate-producing microorganisms like Firmicutes are known to produce SCFAs. In addition, butyrate has the energy that provides 5–15% of the calories needed per individual daily [47, 65]. Therefore, Firmicutes' absence or reduced population in type 2 diabetes could elevate the blood glucose level. The increase in blood glucose is because the host will seek the missing calories by consuming more food. Lack or low butyrate concentration could also reduce satiety, making the host eat more, thus raising blood glucose [30, 47, 66].

Proteobacteria, which are more dominant in type 2 diabetes, induce inflammatory responses [36, 47]. An alteration in PBAC composition is common in metabolic syndromes causing diseases. In a study where the fecal samples of patients with type 2 diabetes were analyzed, a significant number of Enterobacteriaceae, a family from the phylum PBAC, were found [14, 31]. At the initiation of an inflammatory response, specific proteins are released into the bloodstream. These proteins inhibit insulin secretion and build insulin resistance in the body [14, 67].

5.2.3 Gestational diabetes

The profile of GM in women with gestational diabetes is similar to patients who have type 2 diabetes [53, 68]. In a study to determine the onset of dysbiosis in pregnant women, GM was typical in pregnant women in their first semester trimester. However, by the third trimester, the population of Proteobacteria and Actinobacteria increased while butyrate-producing microorganisms like *Faecalibacterium* and *Eubacterium* from phylum Firmicutes reduced. In addition, the Enterobacteriaceae family and *Streptococcus* were also numerous. Even though scientists observed Bacteroidetes and Firmicutes throughout all three trimesters of the pregnancy [68, 69]; however, the strong negative relationship between Bacteroidetes and Firmicutes phyla in healthy pregnant women was missing in women with gestational diabetes [7].

Most of the GM reduced were SCFA producing bacteria. The absence of these bacteria in pregnant women reduced the physiological function of the intestine. The gut permeability was not regulated, insulin sensitivity was reduced, inflammatory response that can lessen the development of diabetes was equally reduced [7]. Gut dysbiosis could be a biomarker for gestational diabetes, and a test of dysbiosis could be early detection before the pregnancy reaches the third trimester [7]. Changes in the GM population was associated with diet and weight gain during pregnancy [53, 68].

5.2.4 Inflammatory bowel disease

The two major bowel diseases associated with dysbiosis are Crohn's disease and ulcerative colitis [14, 15, 23]. In patients with Crohn's disease, the composition of GM was different from healthy individuals. Bacteria belonging to Firmicutes and Actinobacteria were decreased, some of which had a probiotic effect, while PBAC and *Ruminococcus gnavus*, another Firmicutes associated with inflammation, were increased [14, 24, 31, 70]. Increased susceptibility to Crohn's disease is attributed to a lack of the production of SCFAs. The PBAC is signaled as a pointer to instability in the microbiota. Therefore, an increase in the PBA**C** population is found in

people with IBD disease. Even though the exact reason for the increase in PBAC is unknown, it is hypothesized that PBAC, with its inflammatory effect, creates anaerobic conditions in the gut. The beta-oxidation process reduces when proinflammation occurs. Therefore, anaerobic conditions contribute to the growth of PBAC, which are facultative anaerobe, thereby allowing dysbiosis [14, 15]. Anaerobic conditions increase the growth of pathogenic Firmicutes but reduce the population of the beneficial Firmicutes, like the Lactic Acid Bacteria [35, 40]. Another IBD due to dysbiosis is ulcerative colitis [14, 15]. Scientists discovered that *Lactobacilli* were low in composition in patients with ulcerative colitis at an active stage, while the Clostridiales order of Firmicutes was more prominent. High *Escherichia coli* was equally identified in people with active ulcerative colitis. Inflammation seen in IBD is associated with the decreased colonization resistance [14, 15].

Inflammatory Bowel Diseases (IBD) occur when genetic and environmental factors encourage the growth of pathogens that can decrease the population of commensals, thereby causing inflammation [15]. In addition, IBD can occur when there is an unusual immune response against commensal bacteria. For example, sometimes immune cells such as macrophages could not recognize GM and trigger an immune response which attacks the intestinal wall [15]. Hence, Firmicutes and Bacteroidetes decrease while PBAC increases.

5.2.5 Obesity

When the GM composition of healthy and patients with obesity were compared, anaerobic Firmicutes and Proteobacteria were increased in the fecal samples of patients. At the same time, Bacteroidetes decreased compared to a healthy individual. The high ratio of Firmicutes and Bacteroidetes has been linked to obesity [14, 71]. A significant increase in Enterobacteriaceae, PBAC family, was equally found in patients with obesity. This population of PBAC family reduced after the patient lost weight [31]. In a study on mice, a toll-like receptor 5, a sensor that detects microbial infection to initiate an immune response, was deficient when fed with a high-fat diet. The masking of toll-like receptor 5 concealed the changes occurring in the GM, and the body could not produce an immune response to fight the strange invading organisms [51, 72]. Deficiency of this receptor has been linked to hypertension, insulin resistance, and weight gain, though the exact reason for the masking was uncertain [15, 73].

5.2.6 Cardiovascular diseases

Microbiota dysbiosis was related to the development of cardiovascular diseases. A high level of PBAC was found in arteriosclerosis plaque, indicating PBAC has the pro-inflammatory effect that can cause plaque [15, 74]. In addition, some scientists reported that GM converts choline, an essential body nutrient, to trimethylamine, an organic compound. Trimethylamine is further processed in the liver to trimethylamine N-oxide which is known to increase arterial plaques. An increase in arterial plaque can cause arteriosclerosis diseases [14, 15]. In another study, Gammaproteobacteria, a class of PBAC, was connected with endogenous alcohol production linked to the cause of non-alcoholic fatty liver diseases, which is associated with increased risk of cardiovascular failure incidence [75].

5.2.7 Cancer

Inflammation caused by some phylum of GM could create a grave environment for the development and growth of cancer cells. Even though cancer linked to microbiota

so far occurs in body parts that house the GM, notably the GIT, the colon [15, 76]. Commensals sometimes take up pathogenic features when invaded, giving them pathogenic effects; such commensals are called pathobionts. In a study on mice, pathobionts and pathogens contributed to the uncontrolled epithelial cell growth of the colorectal region [15]. Some scientists also suggested that some GM like *Bacillus fragilis*, a Bacteroidetes are virulent and can modify the GM to favor inflammatory responses. These inflammatory responses could cause alterations in the epithelial cells, and this could result in cancer. The inflammatory response will equally allow the invasion of cancer allies' microorganisms [15, 43]. In addition, people with chronic inflammatory disarray have been discovered to have a high susceptibility to gastric cancer and cancer of the lymphatic system associated with the mucosa [76].

6. Conclusion

Research continues on how GM and its activities cause chronic diseases. From completed studies, it is apparent that the composition of the gut differs between diseased and healthy individuals. While a significant population of commensals and SCFAs producing bacteria reduced, the pathogenic population increased and influenced the commensals, making them turn against the host. Pathogens equally created unfavorable conditions such as inflammatory or anaerobic conditions. The change in the environment favored the growth of pathogens but reduced the growth of commensals.

To take care of gut health, the types of food consumed determines the type of GM. Fermentable dietary fibers such as pectin, inulin, and resistant starch undergo fermentation by GM to produce 15% butyrate, 60% acetate, and 25% propionate. Butyrate maintains colonic homeostasis and prevents inflammation, and maintains mucosal integrity [44], thereby playing a role in reducing dysbiosis. Therefore, food rich in these fermentable dietary fibers would be suitable for gut health [25, 44]. The types of protein consumed matter to gut health. Animal protein fermentation decreases the production of SCFAs, increasing the risk of IBD [25]. However, consuming plant-based protein is associated with an increase in beneficial GM like *Bifidobacterium*, *Lactobacillus,* and it increases the production of SCFA [25, 44]. High consumption of polyunsaturated fatty acids has been associated with an increased healthy GM population like *Lactobacillus* and *Roseburia*, thus increasing the production of SCFA-butyrate [25, 44]. In contrast, high consumption of sodium and food additives such as sweeteners are associated with changes in the composition of GM. When food is high in sodium, it reduces the population of commensal microorganisms like *Lactobacillus*. Also, food additives cause a significant change in the population of the balanced gut system [25, 44]. What humans eat can determine gut health, and the composition of GM in the gut contributes to overall well-being.

Asides healthy diet, there are other ways to improve gut health. One of these ways is the use of probiotics as supplements. Probiotics are live microorganisms made into pills that profer health benefits when administered in adequate amounts. In addition, the use of prebiotics has equally been suggested. Prebiotics are not microorganisms but non-digestible substances that benefit the host by improving the growth and activities of selected bacteria in the gut [77–79]. Other methods are requiring medical experts and scientists. One is fecal microbiota transplantation, which involves infusing stool from a healthy donor to a recipient by delivering the stool through the upper GIT [80]. This method requires adequate care to ensure the feces transferred to other patients do not have infectious microorganisms. Other methods being used include phage therapy, bacteria consortium transplantation, and the use of predatory bacteria [81].

Acknowledgements

Special thanks to Olukayode Olubowale and Oluwaseun Sanusi for their contribution to the content of the chapter.

Author details

Temitope Sanusi-Olubowale[1,2]

1 Saybrook University, Oakland, California, USA

2 Albany State University, Albany, Georgia, USA

*Address all correspondence to: olutopy@gmail.com

References

[1] Centers for Disease Control and Prevention. About Chronic Diseases [Internet]. 2021. Available from https://www.cdc.gov/chronicdisease/about/index.htm [Accessed: 2021-04-19]

[2] Stoppler MC [Internet]. Medical Definition of Chronic disease. 2021. Available from https://www.medicinenet.com/chronic_disease/definition.htm [Accessed: 2021-07-10]

[3] World Health Organization. Integrated chronic disease prevention and control [Internet]. Available from https://www.who.int/chp/about/integrated_cd/en/ [Accessed: 2021-04-19]

[4] Barker DJ. Developmental origins of chronic disease. Public Health. 2012 Mar 1;126(3):185-9. DOI: https://doi.org/10.1016/j.puhe.2011.11.014

[5] Centers for Disease Control and Prevention. Health and Economic Costs of Chronic Diseases [Internet]. 2021. Available from https://www.cdc.gov/chronicdisease/about/costs/index.htm [Accessed 2021-04-19]

[6] Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12;97(18):1837-47. DOI: https://doi.org/10.1161/01.CIR.97.18.1837

[7] Ma S, You Y, Huang L, Long S, Zhang J, Guo C, Zhang N, Wu X, Xiao Y, Tan H. Alterations in gut microbiota of gestational diabetes patients during the first trimester of pregnancy. Frontiers in cellular and infection microbiology. 2020 Feb 27;10:58. DOI: https://doi.org/10.3389/fcimb.2020.00058

[8] Baanders AN, Heijmans MJWM. The impact of chronic diseases: the partner's perspective. Family and Community Health. 2007;30:305-317. DOI: 10.1097/01.FCH.0000290543.48576.cf

[9] Bigatti SM, Cronan TA. An examination of the physical health, health care use, and psychological well-being of spouses of people with fibromyalgia syndrome. Health Psychology. 2002 Mar;21(2):157. DOI:10.1037/0278-6133.21.2.157

[10] Abegunde D, Stanciole A. An estimation of the economic impact of chronic noncommunicable diseases in selected countries. World Health Organization, Department of Chronic Diseases and Health Promotion. 2006; 2006. Available from https://www.who.int/chp/working_paper_growth%20model29may.pdf [Accessed: 2021-04-19]

[11] Milken Institute Study. Chronic disease costs US economy more than $1 trillion annually [Internet]. Available from https://www.fightchronicdisease.org/latest-news/milken-institute-study-chronic-disease-costs-us-economy-more-1-trillion-annually. [Accessed: 2021-07-10]

[12] Telford RD. Low physical activity and obesity: Causes of chronic disease or simply predictors? Medicine & Science in Sports & Exercise. 2007 Aug 1;39(8): 1233-40. DOI: 10.1249/mss.0b013e31806215b7

[13] Thursby E, Juge N. Introduction to the Human Gut Microbiota. Biochemical Journal. 2017;474(11):1823-1836. DOI: 10.1042/BCJ20160510

[14] Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. International Journal of molecular sciences. 2015 Apr;16(4):7493-519. DOI: https://doi.org/10.3390/ijms16047493

[15] Blumberg R, Powrie F. Microbiota, disease, and back to health: a metastable journey. Science Translational Medicine. 2012 Jun 6;4(137):137rv7-. DOI: 10.1126/scitranslmed.3004184.

[16] Li N, Ma WT, Pang M, Fan QL, Hua JL. The commensal microbiota and viral infection: a comprehensive review. Frontiers in Immunology. 2019 Jul 4;10:1551. DOI: https://doi.org/10.3389/fimmu.2019.01551

[17] Looi M. The human microbiome: Everything you need to know about the 39 trillion microbes that call our bodies home [Internet]. 2020. Available from https://www.sciencefocus.com/the-human-body/human-microbiome/. [Accessed: 2021-07-10]

[18] National Institute of Health. NIH Human Microbiome Project defines normal bacterial makeup of the body: Genome sequencing creates first reference data for microbes living with healthy adults [Internet]. 2012. Available from https://www.nih.gov/news-events/news-releases/nih-human-microbiome-project-defines-normal-bacterial-makeup-body. [Accessed: 2021-07-10]

[19] McGill M. What are the gut microbiota and human microbiome? [Internet]. 2018. Available from https://www.medicalnewstoday.com/articles/307998 [Accessed 2021-04-19]

[20] Abbott A. Scientists bust myth that our bodies have more bacteria than human cells. Nature. 2016. DOI: https://doi.org/10.1038/nature.2016.19136

[21] Nuli R, Cai J, Kadeer A, Zhang Y, Patamu M. Integrative analysis toward different glucose tolerance-related gut microbiota and diet. Frontiers in Endocrinology. 2019;10(295):1-14. DOI: https://doi.org/10.3389/fendo.2019.00295

[22] Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. Allergology International. 2017 Oct 1;66(4):515-22. DOI: https://doi.org/10.1016/j.alit.2017.07.010

[23] Parada VD, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJ, Faber KN, Hermoso MA. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Frontiers in Immunology. 2019 Mar 11;10:277. DOI: https://doi.org/10.3389/fimmu.2019.00277

[24] Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Reddy DN. Role of the normal gut microbiota. World Journal of Gastroenterology. 2015; 21(29): 8787-8803. DOI: https://doi.org/10.3748/wjg.v21.i29.8787

[25] Robertson, R. 10 Ways to Improve Your Gut Bacteria, Based on Science [Internet]. 2016. Available from https://www.healthline.com/nutrition/improve-gut-bacteria. [Accessed: 2021-06-27]

[26] Kieffer DA, Martin RJ, Adams SH. Impact of dietary fibers on nutrient management and detoxification organs: Gut, liver, and kidneys. Advances in Nutrition. 2016 Nov 15;7(6):1111-1121. DOI: 10.3945/an.116.013219.

[27] De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Backhed F, Mithieux G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014 Jan 16;156(1-2):84-96. DOI: https://doi.org/10.1016/j.cell.2013.12.016

[28] Hugon P, Dufour J, Colson P, Fournier P, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. The Lancet Infectious Diseases. 2015 10;15(10):1211-1219. DOI:10.1016/S1473-3099(15)00293-5

[29] Brogden KA, Guthmiller JM, Taylor CE. Human polymicrobial infections. Lancet. 2005 Jan 15-21;365(9455):253-5. DOI: 10.1016/S0140-6736(05)17745-9

[30] Gerard C, Vidal H. Impact of gut microbiota on host glycemic control.

Frontiers in Endocrinology. 2019;10(29): 1-13. DOI: https://doi.org/10.3389/fendo.2019.00029

[31] Rizzatti G, Lopetuso LR, Gibiino G, Binda C, Gasbarrini A. Proteobacteria: A common factor in human diseases. BioMed Research International. 2017 Oct;2017. DOI: https://doi.org/10.1155/2017/9351507

[32] Noel O. Purple bacteria or purple photosynthetic bacteria are pigmented by bacteriochlorophyll and carotenoids, giving them a colorful range of purples, pinks and oranges. They photosynthesize without producing oxygen as a by-product. This type of bacteria are proteobacteria which are phototrophic (produce their own food via photo-synthesis). [Internet]. Available from https://wellcomecollection.org/works/zermwrgw [Accessed: 2021-07-03]

[33] Stackebrandt E, Murray RG, Truper HG. Proteobacteria classis nov., A name for the phylogenetic taxon that includes the "purple bacteria and their relatives." International Journal of Systematic and Evolutionary Micro-biology. 1988 Jul 1;38(3):321-5. DOI: https://doi.org/10.1099/00207713-38-3-321

[34] Overview of Proteobacteria [Internet]. 2021. Available from: https://bio.libretexts.org/@go/page/9775 [Accessed 2021-04-19]

[35] Encyclopedia of life. Purple bacteria and relatives [Internet]. Available from https://eol.org/pages/311/articles Accessed: 2021-07-09

[36] Satokari R. High intake of sugar and the balance between pro-and anti-inflammatory gut bacteria. Nutrients. 2020;12(5):1-4. DOI: https://doi.org/10.3390/nu12051348

[37] Actinobacteria (High G + C Gram-Positive Bacteria) [Internet]. 2021. Available from: https://bio.libretexts.org/@go/page/9786 [Accessed 2021-04-19]

[38] Anandan R, Dharumadurai D, Manogaran GP. An Introduction to Actinobacteria. In Dharumadurai D, Jiang Y, editors. Actinobacteria - Basics and Biotechnological Applications. Intechopen; 2016. DOI: 10.5772/62329

[39] National Institute of Allergy and Infectious Diseases (NIAID). *Mycobacterium tuberculosis* Bacteria, the cause of TB. Available from https://www.flickr.com/photos/54591706@N02/5149398656 [Accessed: 2021-7-7]

[40] Firmicutes [Internet]. 2021. Available from: https://bio.libretexts.org/@go/page/978 [Accessed 2021-04-19]

[41] Neve H, Rubner M. "File: *Lactobacillus paracasei*.jpg" 2018. Available from https://search.creativecommons.org/photos/728ca0ee-110a-4b06-b639-60444e0a801d [Accessed: 2021-07-07]

[42] Bacteroidetes and Chlorobi [Internet]. 2021. Available from: https://bio.libretexts.org/@go/page/9799 [Accessed 2021-04-19]

[43] Wexler HM. Bacteroides: the good, the bad, and the nitty-gritty. Clinical Microbiology Reviews. 2007 Oct;20(4): 593-621. DOI: 10.1128/CMR.00008-07

[44] Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferri F, Pulcini G, Miggiano GA, Gasbarrini A, Mele MC. Food components and dietary habits: Keys for a healthy gut microbiota composition. Nutrients. 2019 Oct; 11(10):2393. DOI: 10.3390/nu11102393

[45] Chakraborti CK. New-found link between microbiota and obesity. World journal of gastrointestinal pathophysiology. 2015 Nov 15;6(4):110. DOI: 10.4291/wjgp.v6.i4.110

[46] Bai Y, Mansell TJ. Production and Sensing of Butyrate in a Probiotic *E. coli*

Strain. International Journal of molecular sciences. 2020 Jan;21(10):3615. DOI: 10.3390/ijms21103615

[47] Stewart L. What is butyrate and why should you care? [Internet]. Atlas. 2021. Available from https://atlasbiomed.com/blog/what-is-butyrate/ [Accessed 2021-04-28]

[48] Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Advances in Immunology. 2014 Jan 1;121:91-119. DOI: https://doi.org/10.1016/B978-0-12-800100-4.00003-9

[49] Chambers ES, Preston T, Frost G, Morrison DJ. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. Current Nutrition Reports. 2018 Dec;7(4):198-206.

[50] Backhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, Khan MT. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host & Microbe. 2015 May 13;17(5):690-703. DOI: https://doi.org/10.1016/j.chom.2015.04.004

[51] Khan R, Petersen FC, Shekhar S. Commensal bacteria: An emerging player in defense against respiratory pathogens. Frontiers in Immunology. 2019 May 31;10:1203. DOI: 10.3389/fimmu.2019.01203.

[52] Jewell T. What Causes Dysbiosis and How Is It Treated? [Internet]. 2019. Available from https://www.healthline.com/health/digestive-health/dysbiosis [Accessed 2021-04-28]

[53] Crusell MK, Hansen TH, Nielsen T, Allin KH, Ruhlemann MC, Damm P, Vestergaard H, Rorbye C, Jorgensen NR, Christiansen OB, Heinsen FA. Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. Microbiome. 2018 Dec;6(1):1-9. DOI: https://doi.org/10.1186/s40168-018-0472-x

[54] Dereke J. Gestational diabetes: A novel detection strategy [Internet]. Research Outreach. 2019. Available from: https://researchoutreach.org/articles/gestational-diabetes-novel-detection-strategy/ DOI: 10.32907/RO-110-148151

[55] Centers for Disease Control and Prevention. Gestational Diabetes [Internet]. 2019. Available from https://www.cdc.gov/diabetes/basics/gestational.html [Accessed 2021-07-01]

[56] Behboudi-Gandevani S, Amiri M, Yarandi RB, Tehrani FR. The impact of diagnostic criteria for gestational diabetes on its prevalence: A systematic review and meta-analysis. Diabetology & Metabolic Syndrome. 2019 Dec;11(1):1-8. DOI: https://doi.org/10.1186/s13098-019-0406-1

[57] Biospec Nutritionals. Gut health and gastrointestinal (GI) imbalances. Available from https://biospec-nutritionals.com/health-topics/gut-health-and-gastrointestinal-gi-imbalances/. [Accessed: 2021-04-28]

[58] Karst SM. The influence of commensal bacteria on infection with enteric viruses. Nature Reviews Microbiology. 2016;14:197-204. DOI: 10.1038/nrmicro.2015.25

[59] Biospec Nutritionals. Gut health and gastrointestinal (GI) imbalances. Available from https://biospec nutritionals.com/health-topics/gut-health-and-gastrointestinal-gi-imbalances/. [Accessed: 2021-04-28].

[60] Myers SP, Hawrelak JA. The causes of intestinal dysbiosis: a review. Alternative Medicine Review. 2004 Jun;9(2):180-97. Available from https://altmedrev.com/wp-content/uploads/2019/02/v9-2-180.pdf [Accessed: 2021-4-30]

[61] Atlas. Microbiome Testing: What Is Dysbiosis And Do You Check For It? Available from https://atlasbiomed.com/blog/dysbiosis-and-microbiome-testing/ [Accessed 2021-06-13]

[62] Laguipo ABB. Dysbiosis Diagnosis. 2018. [Internet] Available from https://www.news-medical.net/health/Dysbiosis-Diagnosis.aspx [Accessed: 2021-07-10]

[63] Vaarala O. Human intestinal microbiota and type 1 diabetes. Current Diabetes Reports. 2013 Oct 1;13(5):601-7. DOI:10.1007/s11892-013-0409-5

[64] Van Herreweghen F, De Paepe K, Roume H, Kerckhof FM, Van de Wiele T. Mucin degradation niche as a driver of microbiome composition and *Akkermansia muciniphila* abundance in a dynamic gut model is donor independent. FEMS microbiology ecology. 2018 Dec;94(12):fiy186. DOI: https://doi.org/10.1093/femsec/fiy186

[65] Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010 Feb 5;5(2):e9085. DOI: 10.1371/journal.pone.0009085.

[66] Dickson I. Intestinal gluconeogenesis prevents hepatic steatosis. Nature Review Gastroenterology Hepatology. 2020;17:316. DOI: https://doi.org/10.1038/s41575-020-0301-0

[67] Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked? Journal of Biomedical Science. 2016;23(87):1-18. DOI: https://doi.org/10.1186/s12929-016-0303-y

[68] Hasain Z, Mokhtar NM, Kamaruddin NA, Mohamed Ismail NA, Razalli NH, Gnanou JV, Raja Ali RA. Gut microbiota and gestational diabetes mellitus: A review of host-gut microbiota interactions and their therapeutic potential. Frontiers in Cellular and Infection Microbiology. 2020 May 15;10:188. DOI: https://doi.org/10.3389/fcimb.2020.00188

[69] Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Bäckhed HK, Gonzalez A, Werner JJ, Angenent LT, Knight R, Bäckhed F. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell. 2012 Aug 3;150(3):470-80. DOI: 10.1016/j.cell.2012.07.008

[70] Henke MT, Kenny DJ, Cassilly CD, Vlamakis H, Xavier RJ, Clardy J. Ruminococcus gnavus, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. Proceedings of the National Academy of Sciences. 2019 Jun 25;116(26):12672-7. DOI: https://doi.org/10.1073/pnas.1904099116

[71] Gerard P. Gut microbiota and obesity. Cellular and Molecular Life Sciences. 2016 Jan 1;73(1):147-62. DOI 10.1007/s00018-015-2061-5

[72] Feuillet V, Medjane S, Mondor I, Demaria O, Pagni PP, Galán JE, Flavell RA, Alexopoulou L. Involvement of Toll-like receptor 5 in the recognition of flagellated bacteria. Proceedings of the National Academy of Sciences. 2006 Aug 15;103(33):12487-92. DOI: https://doi.org/10.1073/pnas.0605200103

[73] Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328:228-231.

[74] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD,

Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472:57-63. DOI: 10.1038/nature09922

[75] Tana C, Ballestri S, Ricci F, Di Vincenzo A, Ticinesi A, Gallina S, Giamberardino MA, Cipollone F, Sutton R, Vettor R, Fedorowski A. Cardiovascular risk in non-alcoholic fatty liver disease: Mechanisms and therapeutic implications. International Journal of Environmental Research and Public Health. 2019 Jan;16(17):3104. DOI: 10.3390/ijerph16173104

[76] Cheng WY, Wu C, Yu J. The role of gut microbiota in cancer treatment: Friend or foe? Gut. 2020;69:1867-1876 DOI:http://dx.doi.org/10.1136/gutjnl-2020-321153

[77] Dix M. What's an unhealthy gut? How gut health affects you [Internet]. 2020. Available from https://www.healthline.com/health/gut-health. Accessed: 2021-07-15]

[78] Nutrition Division. Health and nutritional properties of probiotics in food, including powder milk with live lactic acid bacteria. FAO Food and Nutrition Paper. 2006;85. Available from http://www.fao.org/3/a0512e/a0512e.pdf. [Accessed: 2021-07-15]

[79] Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. The Journal of nutrition. 1995 Jun 1;125(6):1401-12. DOI: https://doi.org/10.1093/jn/125.6.1401

[80] Kim KO, Gluck M. Fecal microbiota transplantation: an update on clinical practice. Clinical endoscopy. 2019 Mar;52(2):137. DOI: 10.5946/ce.2019.009

[81] Gagliardi A, Totino V, Cacciotti F, Iebba V, Neroni B, Bonfiglio G, Trancassini M, Passariello C, Pantanella F, Schippa S. Rebuilding the gut microbiota ecosystem. International journal of environmental research and public health. 2018 Aug;15(8):1679. DOI: https://doi.org/10.3390/ijerph15081679