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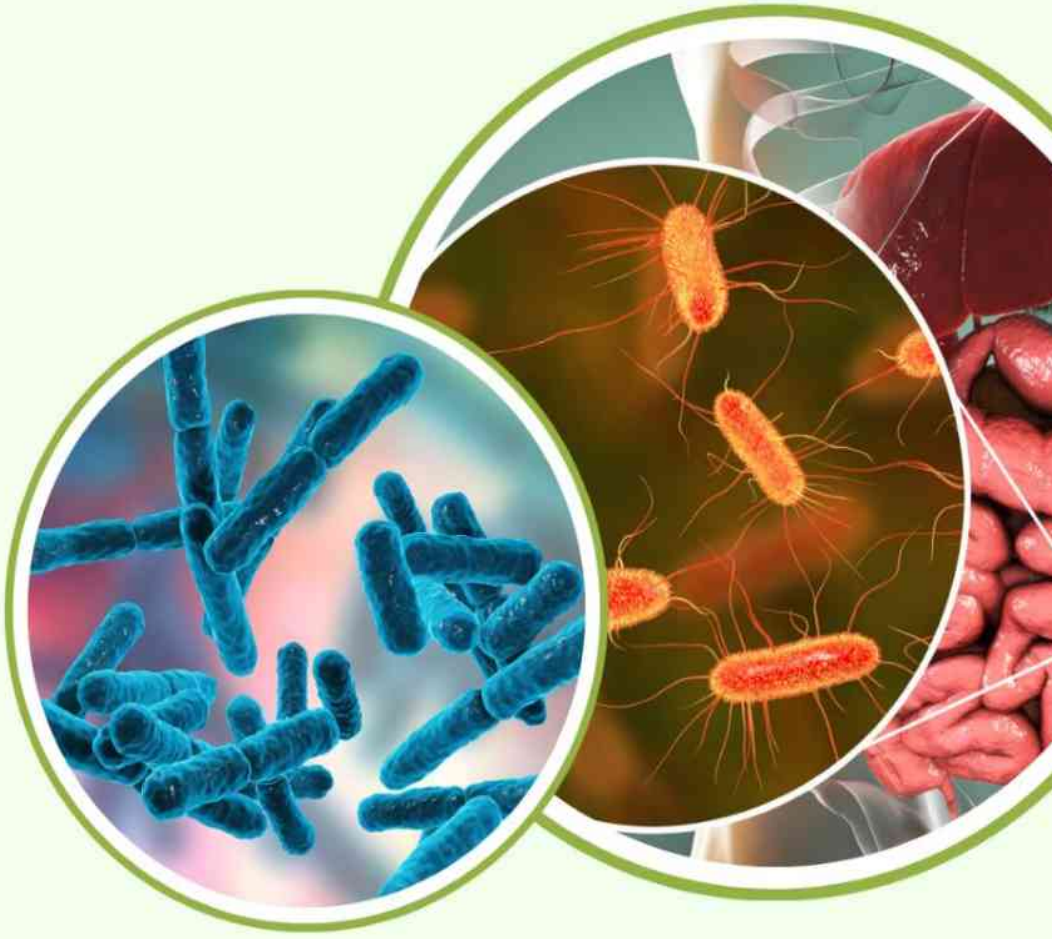
THE HUMAN GUT MICROBIOME: GEOGRAPHY, HEALTH, DISEASE AND THE ROLE OF PROBIOTICS, PREBIOTICS, SYNBIOTICS.



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The Human Gut Microbiome: Geography, Health, Disease and The Role of Probiotics, Prebiotics, Synbiotics.

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Abstract

The human gut carries millions of microbes that characterize a complex microbial community. The geographic variations in gut microbiota composition appear to be driven by changes in diet, lifestyle, and climate. Southern and Northern Europe differ in gut microbiota patterns. In Northern Europe, greater Firmicutes (including Lactobacillus) gut microbiota proportion is associated with higher latitudes and is linked to greater energy extraction, fat storage and possibly obesity. In Southern Europe, there is more variability with different species of Bifidobacteria, in Mediterranean populations, Bifidobacterium longum is more prevalent. Microecologic preparations designed to positively alter gut microbiota include probiotics with Lactobacillus and Bifidobacterium and prebiotic fructooligosaccharides. Changing the gut microbiota is important in the treatment of several dysbiosis associated diseases, obesity and inflammatory bowel diseases (IBD) in particular, because of the need to restore the dysbiotic microbiota, reduce inflammation, and improve the dysfunctional gut barrier. Because clinical outcomes can be unpredictable, more, well-controlled studies are warranted. Geographic factors heavily influence gut microbiota and thus influence the disease susceptibility and the response to probiotics and prebiotics in different European populations.

Key words: Microbiota, Probiotics, Host health, Obesity, Geographic change.

1. INTRODUCTION

The human body is inhabited by a variety of bacteria, viruses, archaea, and unicellular eukaryotes. Microbes reside on all surfaces of the human body, yet many microbes reside in the gastrointestinal tract/gut. The human gut carries roughly over one thousand microbial species that constitute a complex ecological community termed as gut microbiota [1]. The human gut carries millions of microbes that characterize a complex microbial community. The gut microbiota has been described as a critical organ building its multidirectional connecting axis with organs. The gut microbiota axis is in charge of host-microbe relations and functions by communicating with the neural, endocrinal, humoral, immunological, and metabolic pathways. Human health being related to the intestine has long been recognized since Hippocrates remarked, "Death sits in the bowls" in 400 B.C. Numerous researches across the globe have centered around the tremendous influence of intestinal microbiota on human disease and health [2]. They are the main regulators of bodily homeostasis and affect a range of physiological functions including metabolism, barrier homeostasis, inflammation, and hematopoiesis via intestinal and extra-intestinal activities. Indeed, the gut microbiota has recently been classified as a "second organ" because of the multidirectional and communication link, or axes, in the way it connects with other organs via the neural, endocrine, humoral, immunological, and metabolic pathways. Every and any change in the community of microorganisms has not only dietary physiological impacts in the gut, but also plays a role in diseases related to other organs, even though the precise mechanisms and interactions of how gut and organs actually interaction are still not fully realized [3]. The promising possibilities of human microbiota are in its ability to make distinct appetite alterations, increase the harvest of nutrients, and utilize energy from the various components within our foods. Likewise, microbes also have fundamental roles in all aspects of xenobiotic metabolism. In xenobiotic metabolism the various gut microbes, chemically alter the structures of the various components found in food, drugs, pollutants, and pesticides [4]. The interaction between the hosts and microbes is an important piece of the health and disease continuum. The gut microbiota diversity is influenced by the various factors of the host, which include diet, human lifestyle, age, and environmental features. However, as it currently stands, diet is arguably one of the most influential factors (or modifiers) in the modulation of gut microbiota [5]. A large number of studies provide evidence that gut microbiota is implicated in the modulation of immunity, weight gain/loss, energy homeostasis, and obesity related disorders [6].

2. GEOGRAPHY FACTOR

The Guangdong Gut Microbiota Project, conducted in 2018, employed data mining to find that the geographical location of hosts had a much greater effect on gut microbiota than other factors such as age, disease and lifestyle. The primary conclusion of the study highlighted the significant effect of regional disparities on the variation in gut microbiota of populations [7]. Differences in gut microbiota composition between different geographic locations could be due to differences in dietary culture and lifestyle. It has been reported that a geographic gradient was present for gut microbiota in cohorts of European infants, and Northern European infants (i.e. Sweden, Scotland etc.) had higher concentrations of Bifidobacteria and Clostridium spp. while Southern European infants (i.e. Spain, Italy etc.) were more abundant with Lactobacillus and Bacteroides species [8]. Through prolonged coevolution with the host, the gut microbiota has developed a range of protective mechanisms that contribute to host health. However, the phenotypic effects of the microbial community can be context-dependent, exhibiting benefits in certain environments or individuals while being detrimental in others. For instance, Prevotella copri, an abundant fiber-degrading agent in non-industrialized human gut micro biota, has been shown to improve glucose tolerance while potentially exacerbating chronic inflammation depending on the specific environment [9]. The gut microbiota is considered a crucial environmental factor and selective agent influencing mammalian diet, phenotypic plasticity, gastrointestinal morphology, and immune adaptability throughout evolution. Thus, variations in gut microbiota may significantly impact evolutionary outcomes across different interactions between mammalian species and their respective gut microbial communities.

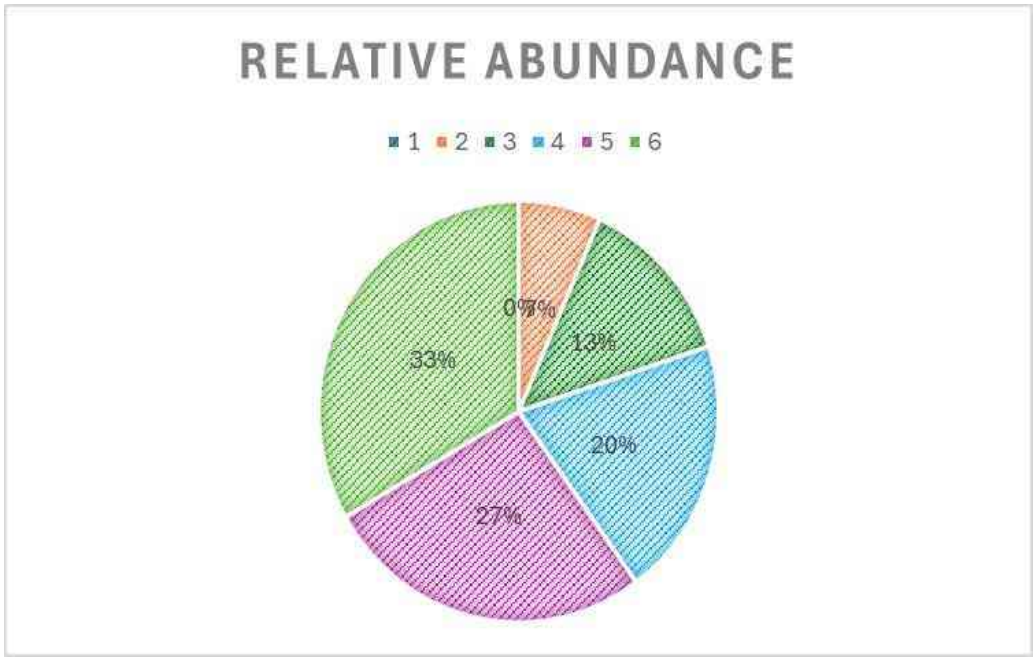

Fig1. Demonstrated the graphic influence on gut microbiota composition with its abundance and area influence by Bifidobacteria clostridium spp. Mainly in Scotland and Sweden as well as Lactobacillus, Bacteroids spp. in Italy and Spain.[10]

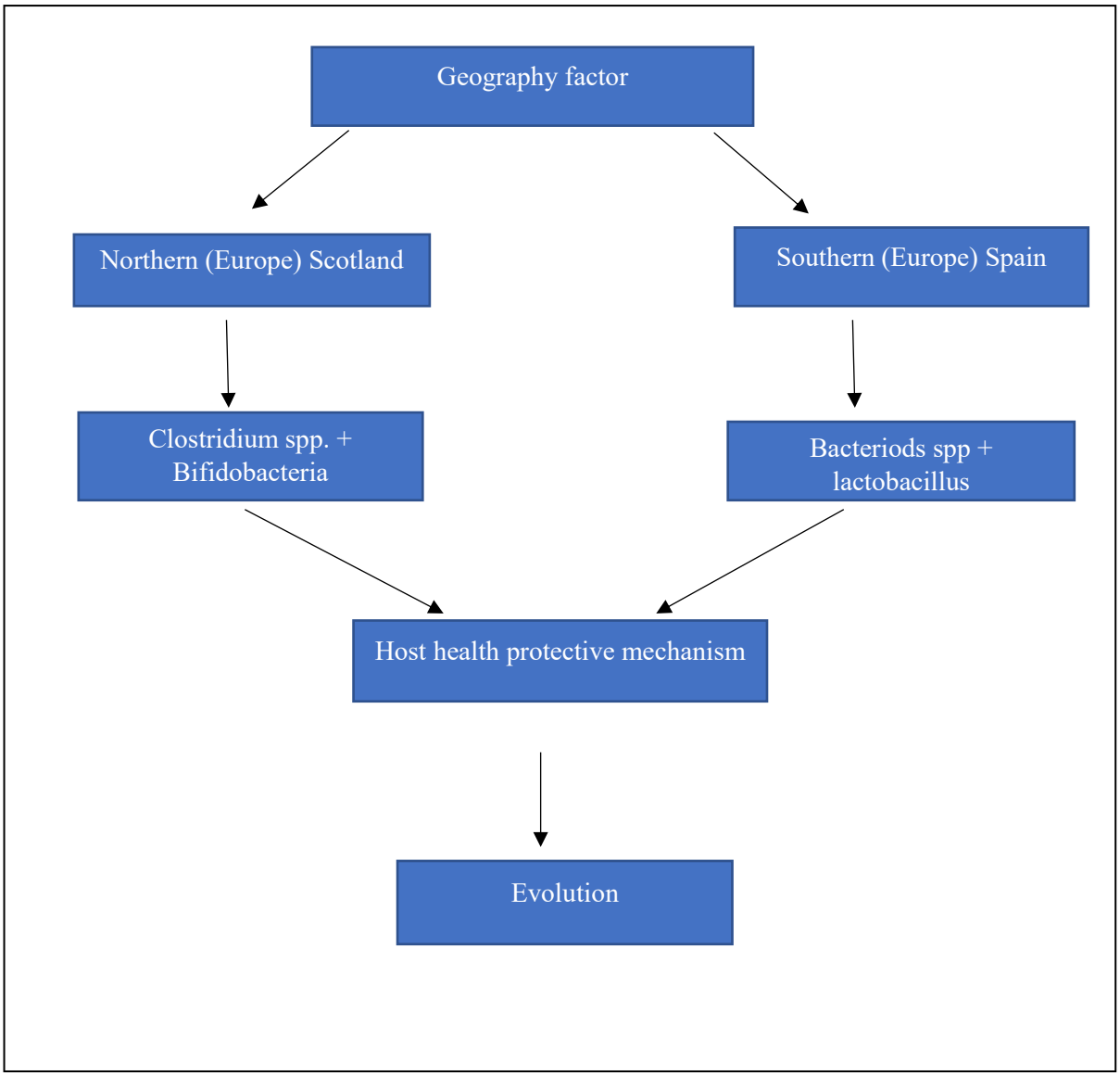

Fig 2. Geography factor- northern and southern (Europe)

3.THE HEALTHY GUT MICROBIOTA

The establishment of the Human Microbiome Project has propelled the detailed examinations of gut microbiota [11,12]. The typical human gut microbiota contains Firmicutes, Bacteroides, Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia with Firmicutes and Bacteroides dominating [13]. The key functional properties of a healthy gut microbiota include the biodegradation of polysaccharides, the production short-chain fatty acids, the enrichment of specific lipopolysaccharides, as well as the production of vitamins and essential amino acids [14]. A healthy and normal gut microbiota is usually characterized as being highly diverse. In contrast, low diversity in the gut microbiota has been associated with disease, including obesity [15]. A second indication of a healthy gut microbiota is that it is in a state of dynamic equilibrium, which means it can resist perturbation, and when it is perturbed, it can return to a healthy state, such as during antibiotic use, [16]. It is known that diet is one of the principal factors in health and disease management and some recent studies have suggested that diet is essential for influencing the gut microbial structure and host metabolism. In turn, the gut environment can promote reproduction, growth, and survival of the microbial community.

4. MICROECOLOGIC PREPARATION

4.1 Probiotic

The term probiotics typically refers to non-pathogenic live microorganisms that are applied to positively affect the microbial balance of the host [17]. Studies have shown that probiotics have significant promise for the prevention and treatment of childhood obesity [18,19]. Probiotic strains such as Bifidobacterium can improve intestinal barrier function [20] demonstrated that treatment with Bifidobacterium breve BR03 and B632 for 8 weeks in individuals aged 6-18 yrs with obesity resulted in weight loss and increased insulin sensitivity. Currently species of Lactobacillus exhibit positive effects in reducing body fat percentage and homeostasis of glucose [21]. Some strains of Lactobacillus and A muciniphila also show strong inhibitory activity against α-glucosidase, preventing the hydrolysis of complex carbohydrates and controlling postprandial hyper-glycemia [22]. In addition, researchers have started to study new probiotics, such as Lactobacillus plantarum 73a (from breast milk) and Bifidobacterium animalis subsp. lactis INL1 [23]. Bifidobacterium animalis subsp. lactis strain BPL1 has been shown to effectively reduce central fat mass in adults with uncomplicated obesity. In a randomized crossover study looking at BPL1 supplementation in children and adolescents with Prader-Willi syndrome, BPL1 was shown to reduce abdominal fat compared to placebo, without affecting total fat mass, which improved fasting insulin levels and insulin sensitivity [24].

4.2 Prebiotic

Prebiotics are types of nondigestible carbohydrates that the gut microorganisms can ferment and utilize as nutrients that aid in keeping the gut microbiota in a healthy equilibrium. Notable prebiotics mentioned in the literature are oligofructose, galacto-oligosaccharide, inulin, and gynolactos [25]. Probiotics primarily regulate lipid metabolism from the effects on the production of beneficial bacteria and SCFAs to maintain intestinal barrier function and increase immunity against inflammation. They may also inhibit lipogenic enzyme activity to decrease lipoprotein and triacylglycerols synthesis [26,27]. Given the positive findings in adults, inulin-based prebiotics have been widely adopted in the research of childhood obesity. For example, the addition of oligofructose-enriched inulin vs the placebo treatment results in the selective modulated the gut microbiota, leading to a remarkable reduction in BMI among children with obesity [28]. The use of prebiotics for the prevention and treatment of childhood obesity must focus on several aspects, including selection of prebiotic type, dose, duration of use, and the correct ratio.

4.3 Synbiotic

The term synbiotic refers to probiotic supplements containing prebiotic components, thus potentially producing a more advantageous effect on gut microbiota than ingesting either probiotics or prebiotics alone. By placing paediatrics participants with obesity into 3 groups with Lactobacillus casei, L casei and inulin, and L casei and fructans, the investigators showed that the combination of L casei with either inulin or fructans significantly improved lipid metabolism and expression of butyrate and propionate, important for gut microbiota modulation [29]. The research on synbiotics remains rather limited. Probiotics and prebiotics demonstrate a short-term efficiency for ameliorating any gut microbiota imbalance from unhealthy states of being. However, one additional caveat is, once the intervention is removed and the patient returns to eating a normal diet, the dominant gut microbiota may gradually cease to exist. Therefore, the integration of many strategies like a balanced diet and soundly designed exercise, in addition to the introduction of probiotics and prebiotics, is optimal to maintain a stable state of gut microbiota with potetial cumulative protective effects on maintenance of the body's metabolism. Probiotics, prebiotics, and synbiotics, as a functional food that is inexpensive and safe, have provided a cutting gedge approach to preventing and/or reducing diet-induced dysregulation of lipid metabolism amid rising healthcare costs attributable to chronic diseases. Probiotics are now widely available in various forms of medicine and health products or edible food forms, including film-coated tablets, powder, capsules, and granulated products. In various developed countries including Japan and Europe, pediatricians commonly recommend probiotic medicines and dietary supplements to child patients [17]. Due to the unique process of child growth and development, generally, probiotic preparations intended for infants and young children should be in liquid or semi-liquid form (e.g., water and milk) and that consideration be given to the choice of media and temperature, as these can impact probiotic activity. Older children can tolerate tablets or capsules well, but chewable probiotic tablets with a pleasant taste are more commonly preferred. Probiotic preparations typically provide a high level of safety; however, adverse reactions have also occurred, including systemic infections, gastrointestinal side effects, skin effects and skin infections, horizontal transfer of genes from probiotics to normal microbiota, stimulation of the immune system, and more. The groups at highest risk include infants, older adults, and those with immunodeficiency as a result of congenital or acquired diseases [30]. Furthermore, although probiotic preparations demonstrate positive effects on human health, it is pertinent to stress that probiotics be used judiciously and not indiscriminately or for prolonged periods of time without any form of assessment.

5. Human diseases by gut microbiota

It is becoming increasingly clear from our new epidemiologic, physiologic and osmic studies, build on by cellular and animal studies, that the intestinal microbiota can play an effective role in both health and disease [31]. Although it is still a very nascent area of study, and much is not understood about the functional features of complex gut microbiota, some exciting studies have been publicized and suggest a vast potential change to the pathogenesis of disease and treatment protocols [32]. Several leading human diseases correlated with a change in the gastrointestinal microbiota, for instance, obesity, diabetes, cardiovascular disease, cancer, hypertension, and IBDs, which would be dealt with in a separate section in this review [31].

5.1 Obesity

Obesity is a myriad and complex metabolic condition with many genetic and nongenetic (environmental) causes. The World Health Organization defines obesity as having a body mass index (BMI) greater than 30 although the specific definitions have significant differences among countries; in China for instance, a BMI of 28 or higher is considered obese. An analysis of all data indicates that

roughly one third of the global population is classified as overweight, and at least 10% as obese [33]. The health threat of obesity as a result of its widespread occurrence makes it an important global health issue. Obesity does not only have changes in appearance but is also associated with lipid and glucose metabolic disorders, pathological inflammation, oxidative stress, and dangerous disease risks especially cardiovascular disease, diabetes, and cancer [34,35]. There up to 100 trillion symbiotic microorganisms harbor in the gut, collectively termed gut microbiota, equal to roughly 10 times the total number of cells in the body [36]. The active gut microbiota will secrete a significant number of physiologically active agents, including short-chain fatty acids, vitamins, and health-promoting products such as anti-inflammatory, analgesic, and antioxidant products, as well as potentially harmful products such as neurotoxins, carcinogens, and immunotoxins [37,38]. Once regarded as a concern of high-income countries, overweight and obesity are increasingly prevalent in low- and middle-income countries. In 2019, almost half of all children aged under age 5 who were overweight or obese live in Asia.

5.1.1 Child obesity

Based on data by the WHO and World Obesity Federation,almost 340million(over 18%)of children and adolescents aged 5~19y worldwide are currently overweight or obese and that figure is rising. The global obesity prevalence among children and adolescents aged 5 to 19y has increased almost 10-fold over the last 4 decades. Therefore, the obesity rate has reached epidemic levels. [39,40]. Once regarded as a concern of high-income countries, overweight and obesity are increasingly prevalent in low- and middle-income countries. In 2019, almost half of all children aged under age 5 who were overweight or obese live in Asia [41]. Many studies have shown that the structures, abundance, and distribution of gut microbiota in the pediatric population are impacted by obesity, which modifies the energy metabolism pathway from a variety of factors, including genetics, exposure of intrauterine microbiota, mode of delivery, and geography. When comparing gut microbiota in children with obesity to normal-weight children, there was a significantly higher abundance of Firmicutes and a lower abundance of Bacteroidetes. After dietary manipulation, there was a reversal in the ratios of these 2 phyla, with subsequent weight loss. Overall, changes in the ratio of intestinal Bacteroidetes and Firmicutes may be associated with childhood obesity [42,43]. The dysbiosis of gut microbiota might be an important factor contributing to childhood obesity. Studies have shown that gut microbiota-targeted therapeutic approaches generally have a clear beneficial effect on childhood obesity. Particularly, the treatment of obesity using dietary manipulation, probiotics, and fecal microbiota transplantation (FMT) are areas of active research. [44]. Nonetheless, the considerable interindividual differences in gut microbial composition and the natural variability of microbial composition, gene expression, and function in an individual also add to this complexity, and add to the challenges in defining the complex relationship between gut microbiome and childhood obesity and its mechanisms of action [45]. The gut microbiota is essential for many of the physiologic homeostatic processes in the host, including fermentation of non-digestible dietary substrates as well as cholesterol and bile acid metabolism and indirect regulation of mood and social behavior via the gut-brain axis (GBA). However, any disturbance of this fine balance resulting from changes in quantity or composition of gut microbiota may ultimately lead to a range of diseases, including inflammatory bowel disease (IBD) and cancers of the gastrointestinal tract [46].

5.2 Hypertension

Hypertension poses an emerging risk to public health and an important risk factor for diseases involving the heart, stroke, and kidneys [47]. Some studies have indicated that many genetic, environmental, and lifestyle factors (sodium intake, physical activity, and alcohol consumption) can contribute to the progression of hypertension [48]. There has been indication of various mechanisms that explain the association between gut microbiota and blood pressure, yet, none have been definitive. Notably, the composition ratio of Bacteroidetes and Firmicutes in gut microbiota has been statistically correlated with hypertension [49]. Hypertensive animals and 7 hypertensive patients' gut microbiota was tested by 16S ribosomal RNA sequencing and observed an abundance of Bacteroidetes and Firmicutes [50]. SCFAs are necessary for gut microbiome homeostasis as well as playing an important role in the host

immune system. Recently published studies have reported SCFAs produced by gut microbiota are involved with blood pressure regulation [51]. SCFAs are able to stimulate host G-protein-coupled receptor (GPR) pathways that regulate the secretion of renin and blood pressure [52]. While another similar study investigated the relationship between serum metabolites and hypertension; the researchers found higher levels of lyxose (a by-product of fermentation in intestinal microbes) in patients with newly diagnosed hypertension compared to healthy controls [53].

However, these findings are preliminary; it is essential to validate other environmental factors like the diet that might affect the gut microbiota.

5.3 Cardio vascular diseases

Despite current preventive strategies and treatment options for atherothrombosis, cardiovascular disease remains the global leading cause of morbidity and mortality, and will ultimately continue to rise as incidence rates escalate in low and middle-income countries [54]. Furthermore, as illustrated above, the intestine has also been recognized as an organ involved in the pathophysiology and progression of CVDs. This is most frequently cited as being due to the reduced perfusion of the intestines leading to intestinal barrier dysfunction following an acute coronary syndrome event. There are many mechanisms of a well balanced intestinal microbiota that regulate the intestinal endothelial barrier [55]. More recently, intestinal microbiota specifically as it relates to an individual's contribution to heart disease and stroke has been studied based on mounting evidence [56]. Furthermore, a previously identified significant relationship between the quantity of fecal gut microbiota as well as the intensity of intestinal permeability was previously demonstrated in patients with CVDs [57]. By contrast, patients with bacteria DNA in peripheral blood had very high levels of inflammatory markers in plasma, especially highly sensitive C-reactive protein and interleukin-6, when assessed against patients with no bacterial DNA in peripheral blood [58]. Also, there is a link between increased abundance of Streptococcus and Enterobacteriaceae with coronary artery disease [59]. Coronary artery disease patients have altered species abundance of the most abundant bacteria that are present in gut microbiota, with the decrease in Bacteroidetes and increase in Firmicutes. Trimethylamine-N-oxide is a metabolite that greatly affects atherosclerosis and can be used as marker to predict cardiovascular risk [60].

5.4 Inflammatory bowel diseases

Inflammatory bowel disease is a prevalence disease that is most common in western nations; its incidence has rapidly increased in newly industrialized nations in Asia, the Middle East, Africa and South America [61]. It will also be important to explore the precise etiology and pathogenesis of IBD. Over the past few years, substantial advances have been made in understanding the pathogenesis of IBD. The most important and clinically useful advancement was the identification of gut microbiota as a multifunctional inflammatory factor related to inflammation. Recently, the role of intestinal microbiota as related to the pathogenesis of IBD has been highlighted. There are numerous lines of evidence highlighting the crucial role of gut microbiota on intestinal inflammation. Most studies highlight a decreased diversity of intestinal microbiota in patients with IBD [62]. The most notable changes to gut microbiota composition are significant reductions in Firmicutes and proteobacteria observed in patients with IBD. The limited diversity of intestinal microbiota in patients with IBD are likely due to the reduced Firmicutes. The reduction of Clostridium leptum groups, particularly F. prausnitzii, have been reported among Firmicutes [63]. The overwhelming majority of identified human pathogenic bacteria are Proteobacteria and the phylum is thought to be involved in IBD [64]. The analysis of microbial diversity also indicates an increase in the number of bacterial species affiliated with this phylum, suggesting it was very likely involved in initiating chronic inflammation when compared to the diversity reports for IBD [65]. Additional clinical studies will be needed to explore and fully understand the fourteen mechanisms that gut microbiota may contribute to IBD progression.

NAME OF DISEASES	FUNCTION	REFRENCE
Obesity	The active gut microbiota will produce a large number of physiologically active substances, including short-chain fatty acids, vitamins, and health-beneficial products such as anti-inflammatory, analgesic, and antioxidant products, along with potentially harmful products such as neurotoxins, carcinogens, and immunotoxins.	37
Hypertension	The epidemiology of hypertension is characterized by high incidence, high disability rate, high mortality rate, and low awareness rate.	66
Cardiovascular disease	In the pathophysiology and progression of CVDs, the intestine has also been involved, primarily due to decreased perfusion of the intestines leading to intestinal barrier dysfunction.	55
Inflammatory	The most significant and clinically beneficial aspect of this advancement was the identification of gut microbiota as a crucial multifunctional inflammatory factor.	62

Table 1: Disease and its function

6. Disease transfer

6.1 Child birth

The mode of delivery is a crucial aspect of vertical transmission of gut microbiota. As the largest genomic investigation on neonatal microbiota to date has shown, there are substantial differences in gut microbiota composition for infants delivered vaginally compared to those delivered by cesarean section [67]. For infants delivered vaginally, the composition of neonatal gut microbiota was similar to maternal vaginal and skin microbiota, reflecting a dominance of Lactobacillus followed by members of the genus Prevotella. Bifidobacteria emerged as the most dominant member onward from days 4–7 of postnatal age with the greatest relative abundance. Generally regarded as critical early colonizers, these microbiomes including species of Bifidobacterium and Lactobacillus are responsible for immune programming and establishment of healthy symbiosis with the human host during early infancy.

Members of the species of Bifidobacterium are capable of synthesizing fucosyllactose, acetate, propionate, and 1,2-propane diol through cross-feeding interactions as they grow off microbial communities. This will subsequently lead to the promotion of immune tolerance toward symbiotic bacteria during development [68]. New born through cesarean delivery have a colonizing microbiota which has components derived from maternal skin and the hospital environment, specifically colonies of Enterococcus, Enterobacter, and Klebsiella species [69]. noted a low abundance and diversity of Bacteroidetes, combined with a high diversity of Firmicutes, present in the intestines of neonates delivered by cesarean section. Where a 16-y longitudinal cohort study found the risk of obesity development to be significantly higher in children delivered via cesarean than in those delivered vaginally; whereas, mothers with a prior history of cesarean delivery, offspring delivered via vaginal birth had 31% lower risk of obesity development compared to those delivered via subsequent cesarean delivery [70]. found that neonates delivered via cesarean section had 1.83 times the risk of being overweight by age 11 than those children delivered vaginally. Moreover, a prospective cohort study started the precedent that cesarean delivery is associated with weight gain in male and female infants within the Yucatec Maya, but only males born through cesarean delivery in the Toba/ Qom were observed to have weight gain from the year one. These findings suggest that the possibility of developing weight gain through cesarean delivery is plausible, but geographical location, as well as gender, should be taken into consideration [71].

6.2 Feeding

Breast milk-fed infants' gut microbiota was dominated by bifidobacterial. In other words, bifidobacterial are of particular significance, as markers of healthy infant gut microbiota, and are known to help with glucose tolerance and reducing intestinal inflammation. In contrast, the formulation-fed infant population were characterized by a diminished dominant lineage of bifi-dobacteria as a microbial community in the intestinal tract, coupled with an increased proportion of bacteria such as E coli and Clostridium spp [72]. While formulas cannot completely replace breastmilk, improving the utilization of formulas with essential components that resemble breastmilk would be a distinct advantage for infant health. In particular, human milk oligosaccharides, are one of the primary metabolic components of breast milk, have been known to impactly beneficial bacteria by promoting the growth of Bifidobacterium and Lactobacillus spp in the gastrointestinal tract changing their dynamic in infant gut micro-biota composition [73]. For some mothers, formula feeding may be the only option available. In the case that formula milk was to be used, formula milk with oligosaccharides was seen to be the best possible alternative. A randomized controlled trial by Liber et al [74]. demonstrated that a combination of 3 oligosaccharides could increase bifidobacteria levels in infant gut microbiota compared to increasing sole prebiotics. Gut microbiota of mixed-fed infants were more similar to infants fed solely formula milk. The use of formula milk alongside breast feeding may also increase the proportion of Firmicutes which is related to increased risk of early-onset obesity based on feeding practices. [75].

7. Diet and behavior

Changes in diet structure exert a more robust regulatory effect on the gut microbiota composition than genetic factors do, predisposing to the colonization by gut microbiota according to dietary habits, which are one of the most important drivers of microbial community structure [76,77]. has shown that the Western diet, high in lipids and glucose, has decreased the abundance of the genus Prevotella in gut microbiota and played role in childhood obesity. In contrast, children on carbohydrate-sufficient diets increased Prevotella abundance and decreased Bacteroides abundance in gut microbiota, whereas vegetarians generally displayed greater abundance of Prevotella and increased Prevotella/Bacteroides ratios than all other diet groups as a result of improved leptin-induced glucose metabolism from dietary fiber. Studies indicated that high-fat or high-carbohydrate diets can promote GBA activation of microglia cells to produce IL-1β, IL-6, and TNF-α to generate an inflammatory response in basal

hypothalamus region of the CNS, promoting leptin resistance in the CNS and therefore insulin resistance, T2DM development. On the other hand, researchers found that it activates protease-activated receptors in intestinal epithelial cells that plays a role in the downregulation of tight-junction proteins occludin and zonula occludens-1 in the intestinal epithelium, which disrupt the mechanical barrier of the mucosa and increases the penetrability of the intestinal wall contributing to intestinal inflammatory diseases [78,79]. The authors have shown in experiments with adolescent mice (4 wk old) that food intake and trends in neuronal activity of the brainstem dorsal vagal complex within 24 h show that HFD neural inputs disrupt circadian regulated brain neurons associated with satiety. Reduced neural stem cell rhythmicity hypothesized increased total food intake that ultimately led to overeating and obesity [80]. Presently some food additives, specifically preservatives, emulsifiers and artificial sweeteners decrease the diversity of gut microbiota leading to an increased risk of adolescent obesity. For example, propionic acid and sodium and calcium salts (organic acid food preservatives), are a specific class of metabolic disruptors that increase the risk of T2DM and obesity in people [81]. Emulsifiers, specifically polysorbate-80 and carboxymethyl cellulose, have been indirectly related to mild inflammation, obesity, and other chronic inflammatory diseases [82]. In addition gut microbiota composition in children < 3y of age is related to the their behavioral characteristics. Bacteria on the surface of breast skin can infect the infant's gastrointestinal tract while breastfeeding [83].

Conclusion

Probiotics have become increasingly important as a health, disease, and nutrition issue worldwide, both scientifically and commercially. Scientific focus has shifted from prospective studies to clinical trials, as researchers want to better understand how microbiota can contribute to our manifestation of health and disease. Eubiosis is important in citizens realizing the health endorsing benefits of probiotics. An unhealthy food intake, such as low fruit and vegetables intake, and abuse of antibiotics can lead to dysbiosis. In a nutshell, probiotics have potential influences in the treatment of common infectious diseases, GI tract dysbiosis, inflammatory diseases, and obesity and diabetes control. Progress in gut microbiota modeling and analysis may expand our understanding of how microbiota influence health and disease, and thus adapt current and future therapeutic and preventative strategies. Recognizing and understanding the specific roles that gut microbiome plays in influencing our growth and development as well as functioning in health and disease, can help us lead better lives, from a better protocol of formula for infants, to new strategies in obesity and cancer, etc. As gut microbiota is such a complex subject, for better understanding of gut microbiota, we suggest and look forward to multidisciplinary approaches in future research.

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