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Review Article

Navigating the Complexities of Leaky Gut Syndrome: Insights into Mechanisms and Implications

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Abstract

Leaky gut syndrome (LGS) is based on the concept that due to certain environmental factors and diseases the intestinal permeability enhanced. This is a hypothetical condition, that is still not being recognized in medical diagnosis. However, the causes and consequences of enhanced intestinal permeability have always been associated with the development of certain ailments, disorders and diseases in humans. Although the problems begin with the digestive system, it affects the entire body as well. While some of the reasons of leaky gut syndrome have been dysbiosis, poor diet, stress and the toxic overload in body, the symptoms developed as a consequence of the leaky gut in humans are as digestive disorders, seasonal and food allergies, bacterial overgrowth, chronic fatigue, skin and autoimmune diseases and arthritis with joint pain. The present paper deals with the study of nature and composition, maturation, mechanism of leaky gut development and the identity of gut microbiota in human.

Keywords: *Human Gut Microbiota; Composition; Maturation; Mechanism; Dysbiosis; Enhanced Intestinal Permeability; Leaky Gut*

Introduction

Leaky gut is an hypothetical condition usually not recognized in medical diagnosis as the concept of enhancing the permeability of intestinal walls due to some environmental factors including certain substances, foods ailments, disorders and diseases. It refers to the increased gastrointestinal permeability allowing the several substances entering the blood stream breaking the epithelial barrier made of tight Junctions. These tight Junctions are in fact regulate the kind of substances to come in and out of the intestines [1-5].

Our gut is full of nearly 100 trillion microbes, about 10X the number of human cells comprising of more than 50 phyla mainly including *Proteobacteria, Actinobacteria, Bacteroidetes* and *Firmicutes*. However, gastrointestinal tract (GIT) is also colonized by fungi and viruses. The microbial colonization of the gastrointestinal tract begins at birth that progressively stabilizes in due course of time. The gut microbiota, in fact is a component of gut barrier performing their important functions as symbiosis, metabolism and the absorption of nutrients. The gut microbiota is more or less in state of ecobalance. However, they are constantly being fluctuated at different time intervals [6-8].

Similarly, the gut-brain axis is composed of the vagus nerve, several hormones, immunity and bacteria. It has been reported that this is also affected by the surrounding stress, diets and the various chemicals of the environment. If this gut-brain axis does not work properly it may develop certain ailments and diseases in human. Some of them are anxiety, depression, autism, obesity and irritable bowel syndrome (IBS). If left untreated it may cause other problems as well [9-11].

Moreover, often overlooked the leaky gut syndrome is now considered an actual condition that affects many more people today. It occurs when the inner lining of the intestine becomes more permeable allowing restricted substances to pass into the blood meaning the guts let more than water and nutrients through- they "leak". Further, in recent past, after the launch of human microbiome project (HMP) studies on gut microbiota in relation to human diseases, therapeutics, chemotherapy, radiotherapy and surgery have become the focus of researchers globally [12].

The present review is an attempt to discuss the leaky gut syndrome describing the nature and composition, maturation, mechanism of leaky gut development and the identity of gut microbiota in human in the light of recent researches done so far in the field of medical microbiology and gastroenterology. This is a comprehensive synthesis of research conducted thus far in the realm of the leaky gut syndrome in human. This is meticulously crafted, drawing upon a multitude of scholarly articles previously disseminated in both national and international academic Journals within the same discipline. The present study is based on a literature review carried out from articles selected by the criteria of relevance.

Composition of gut microbiota

The human gut is a complex ecosystem comprising of trillions of microorganisms predominantly found in colon reaching 3.8 X 10^{13} microbes outnumbering the host cells as 3 X 10^{13}. These microbes comprised of 160 species categorized in 5 major phyla named as *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria* and *Verrucomicrobia*. *Bacteroidetes* and *Firmicutes* are the two dominating phyla representing 90% of the human gut microbiota. Further, the human gut is composed of over 99% of anaerobic bacteria. Similarly, the bacteria accounts 60% of the dry mass of the human feces [13,14]. Similarly, the genera of bacteria that predominantly found in human's GI tract are *Lactobacillus, Bifidobacteria, Clostridium, Streptococcus, Escherichia, Ruminococcus, Eubacterium, Porphyromonas* and *Prevotella.* In addition to bacteria, several other groups of microorganisms are also found in GI tract of human. They are fungi, yeast, archaea and viruses [15].

Maturation of gut microbiota

The maturation of gut microbiota takes place before reaching a rather more stable state of composition. It varies greatly during the first year of life. The early colonization of infants gut microbiota begins with the vaginal delivery. It evolves very rapidly during the first year of life But a baby born via caesarian section, the gut microbiota is first colonized by the mothers skin and environment. It mainly comprised of *Clostridium coccoides* group, *C. botulinum* group, *Bacteroides, Veillonella* and *Akkermansia muciniphila.* Similarly, the maturation of gut microbiota into an adult depends up on the various factors like diet age, medicine, gut wall structure and physiology, exercise, genetics and environment. An adult healthy human gut microbiota is usually composed of *Bacteroidetes, Firmicutes, Actinobacteria* and *Proteobacteria* [16]. Finally, a healthy human gut consists of 8 phyla, 18 classes, 23 orders, 38 families, 59 genera and 109 species. Numerically, 31 with 19.7%, 32 with 20% and 63 with 40% belong to as the members of *Bacteroidetes, Actinobacteria* and *Firmicutes* respectively (Table 1) [17].

Nature and identity of gut microbiota

Our body is full of trillions of microorganisms often called as microbiota of thousands of different species. It consists of bacteria, fungi, parasites and viruses. In a healthy person, these bugs coexist peacefully with the largest members residing gut. The gut is a best studied site of human microbiome featuring densest and diverse microbial community of the human body. It acts like a bioreactor extracting energy, vitamins and nutrients from the foods we consume. It also helped us in digesting rest of the undigested foods that we cannot digest of my own [14,18,19].

Bacteroides fragilis	*Clostridium butyricum*	*Rickettsia rickettsiae*
Bacillus cereus	*Clostridium perfringens*	*Shigella dysenteriae*
Bacillus anthracis	*Clostridium tetani*	*Salmonella enterica*
Bacillus canis	*Escherichia coli*	*Staphylococcus epidermis*
Bilophila wadsworthia	*Enterococcus faecalis*	*Staphylococcus saprophyticus*
Brucella abortus	*Enterococcus faecium*	*Staphylococcus aureus*
Brucella melitensis	*Fusobacterium nucleatum*	*Streptococcus pneumoniae*
Brucella suis	*Giardia lamblia*	*Streptococcus* agalactiae
Campylobacter Jejuni	*Helicobacter pylori*	*Treponema pallidum*
Chlamydia pneumoniae	*Haemophilus influenzae*	*Vibrio cholerae*
Chlamydia trachomatis	*Klebsiella pneumoniae*	*Yersinia pestis*
Clostridioides difficile	*Leptospira interrogans*	*Yersinia enterocolitica*
Clostridium botulinum	*Listeria monocytogenes*	
Clostridium bolteae	*Mycoplasma pneumoniae*	
Proteus mirabilis		

Table 1: *A list of human gastrointestinal known pathogens. (Source: Adapted from King., et al. 2019) [17].*

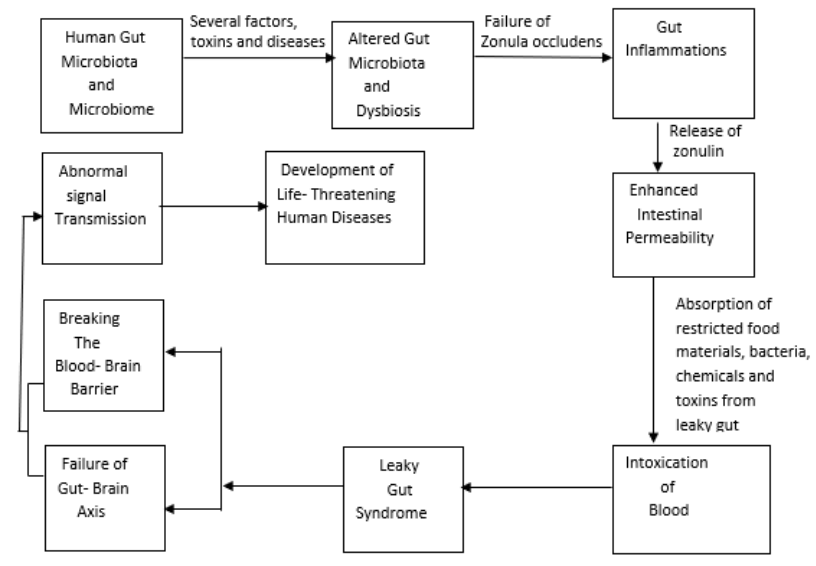
Normal gut microbiome is a set of certain microbes established consistently in an healthy individual. This is quite variable depending upon geography, race, age, diet and various other environmental factors including the life style and so on. This is again fluctuated daily, weekly and monthly depending on a host of various environmental factors like diets, medication, exercise, age, genetics and physiology of gut and the gut wall structure [20].

Though the microbiome carried out many functions, the gut microbiota is different from person to person. That is why the liking and disliking of any two persons are not exactly the outcome of the same feeling. The quality and amount of gut microbiota is different from person to person depending upon the various factors involved. In fact, the individualized quality and amount of microbiota might be matched with the nature and habit of an individual and in turn hypothetically be signatured for their identity in nature. This is a matter of further research. If it could have been possible it will be a powerful tool for the identification of an individual forensically and microbiologically in future [21-23].

Mechanism of leaky gut development

While microbiota is simply an assembly of different microorganisms living together in a particular habitat as the human gut, the microbiome is described as a community of different microorganisms each other and the occupied environment as well [6]. Similarly, the gut- brain-axis is a two way link that communicates gut to the CNS. Therefore, the gut microbiome is often regarded as the “second brain” of the human body. It not only includes the gut microbiota but their network is well extended to the anatomy and metabolism, endocrine, immunity and humoral systems of the brain and body [11,24].

The connection between gut dysbiosis and the development of CNS disorders has been proved in a recent decade. The increased intestinal permeability caused by the altered gut microbiota and the entrance of several substances, bacteria and toxins induce the gut inflammations affecting the human organs including spinal cord and brain. The gut-brain axis plays a key role for the integrity of intestinal epithelial barrier. Zonulin, a tight Junction regulator also plays a good role in maintaining the function of blood-brain barrier. The altered intestinal release enhanced the permeability of intestinal mucosa to enter the various substances in the blood system developing several ailments and diseases in human (Flowchart 1) [2,11,25,26].



Flowchart 1: *Schematic representation of alteration of gut microbiota developing diseases in human.*

A tight Junction or zonula occludans is a kind of protein complex Joining the two epithelial cells to prevent the leakage from intestinal membranes. A zonula occludans secreted zonulin, a kind of haptoglobin 2 precursor that increases the permeability of intestinal membranes. This is for the first time discovered by the Alessio Fasano in the year 2000. Zonulin has also been implicated in the pathogenesis of *Vibrio cholerae* infection in human, celiac disease and diabetes mellitus type 1 and 2 [1,25,27-30].

Conclusion

The human microbiota is estimated to be 10^{13} - 10^{14} microbial cells with around 1:1 ratio the number of human cells. The normal gut microbiota comprised of two major phyla named as *Bacteroidetes* and *Firmicutes* followed by the *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Verrucomicrobia*. The first two major phyla constitute the overall 90% microbiota of the total intestinal microbiome. The human gut harbours about 100 trillion microbial cells. Similarly, it has been estimated that our gut contains 100x more genes than the genes found in human genome comparing of about 1000 bacterial species. While a microbiota is an assembly of different microorganisms living together in a particular habitat such as the human gut, the microbiome on the other hand is an outcome of microbial functions interacting each other and surrounding the environment.

The leaky gut syndrome is an hypothetical medical condition still not recognised as an independent disease. However, in leaky gut syndrome, the enhanced permeability of intestinal walls has been documented in certain human diseases. Similarly, certain environmental, psychological, toxic substances and pathogenic microbes have also been involved in increasing the intestinal permeability allowing them to enter in the blood. These substances after crossing the blood-brain barrier also developed various neurodegenerative diseases in human. Scientists are still working in diagnosis and the treatment of leaky gut syndrome. More researches are still required to better understand the mechanisms and implications of LGS in human.

Last but not the least, several scientists have already been engaged in examining the status of gut microbiota with the help of concerned poop excreted. Recently the same Job is also being carried on in many commercial laboratories. But unfortunately, since these works are in a juvenile stage, they are still not being fully acceptable in the medical field.

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Ethical Clearance

As this is purely a review article, therefore, it does not require any ethical clearance.

Conflict of Interest

There is no conflict of interest with this manuscript.

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