



Review Article

Importance of dietary intake and immunity in this global pandemic: in the perspective of microbiome makeup

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Abstract

This article suggests the importance of the microbial makeup of our body and how it impacts the immune system and influence of diet towards the microbiome and vice versa. The dietary effects that possibly modulate innate and adaptive immunity are essential to managing this global pandemic. Furthermore, usage of probiotic products and how it directly powers the microbiota and its metabolites to have a positive convergence with gut cells are discussed here. This article gives an insight into the microbiome and its consequence in immunity that has a direct and indirect influence.

Keywords adaptive immunity, dietary changes, innate immunity, microbiome, probiotics

Introduction

Good digestion is the best nutrition, it is an age-old epigram told by our ancestors. They had a clear insight into the preparations, ingredients, and quantity of each ingredient to be included in each food and are sought to us through various inscriptions and books. All would have heard these axioms to eat wholesomely, relax at your meals, chew thoroughly, and don't drink between meals. Are we aware that it is all connected to our health system? Especially, we have to take care of the microbes. It may sound crazy that how the microbiome makeup of a person may influence the body. Many studies show that alterations in microbiota resulted in weight gain without a change in food quantity or quality. What goes inside our body doesn't say the whole story. The efficiency of the digestion affects our resulting health and energy levels greatly. The digestions of foods are greatly influenced by the Microbiota present inside our system.

An extended view of ourselves as a life form in terms of the found microbiota may vary extravagantly among each one of us. The genes encoded by the gut microbiota, the gut microbiome, outnumber the human genome by 100:1. This complex ecosystem is formed mainly by bacteria, but also by viruses, archae, protozoa, and fungi. Our microbial population exceeds the total number of our cells by many folds and thus, it becomes a fundamental fragment of our genetic landscape.

Food thy works

Diet is a prominent factor that shapes gut microbiota. Essentially, there exists a dynamic interrelationship between diet, gut microbial ecology, and energy balance. A slight variation in intestinal bionetwork and its manifestations affect the efficiency of the harvest of nutrients and energy from the foods we consume. Digestion and uptake of the food components by the human host

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are greatly influenced by gastrointestinal function and health, whereas the non-digested food components are monitored by the diversity and activity of gut microbiota. The cellular binding and specific response of the nutritional components, transformation of food components, and production of short-chain fatty acids are performed by the gut microbiota while the human host acts as an endogenous substrate-mucus for those actions to be achieved. Hence, there exists a strong interrelation between the human host and intestinal microbiota.

Microbial population map in the human host

Microbial biomass is found in every part of our system. Its maximal number exist in colon region (10^{11} cells/ml) where pH is in the range of 5-7. Ileum contains 10^8 cells/ml and has a pH of 7-8. Jejunum has a pH of 7-9 and it has 10^{4-5} cells/ml whereas the duodenum contains 10^{3-4} cells/ml with a pH of 5-7. In the stomach region pH is highly acidic ie, 1.5-5, even in these conditions 10^{2-3} cells/ml exist.

Major bacteria phyla and genera predominating in human gut microbiota in normal health conditions

Most of the gut organisms are strict anaerobes and they are hard to culture *in vitro* [1]. But now highly sophisticated techniques are available to study these uncultured microbes to have clear understanding of the mechanism of action.

Generally, during the gestation period, the gut of the fetus is almost sterile and it functioning depends on the food consumed by the mother and type of delivery. *Bifidobacteria*, *Bacteroides*, *Staphylococcus*, *Corynebacterium*, *Propionibacterium* Spp dominates in cesarean delivery, and in vaginal delivery, the child gets the organism through the microbiota present in the vaginal region of the mother, that usually constitutes *Lactobacillus*, *Prevotella*, *Sneathia* Spp, *Clostridium difficile*.

During the first few months of infants, *Enterobacteria* tends to increase; however, by 6 months of age, *Bifidobacterium*, *Bacteroides* inclines in gut microbial populations. After weaning of babies possibilities of diversification of microbiota increases and thereby 24 months of *Firmicutes* and *Bacteroides* takes lead in growing inside the gut. Throughout the positive energy balance from school going age to adolescents till adulthood *Firmicutes* tend to predominate and again it purely depends on quality and characteristics of diet consumed, but while we are in negative energy balance *Firmicutes* decreases and *Bacteriodes* commence to increase according to Kumar et al., [2].

Microbiota in health symbiosis

We provide shelter and nutrients for the microbes, inturn, they increase the metabolic capacity (to digest plant carbohydrates, milk sugars), provides vitamins (B2, B12, K, Folic acid), and protect us from colonization of pathogens (colonization resistance). Food is a mixture of various components; SCFAs, acetate, and butyrate are reported as the end products of microbial mediated degradation of proteins and carbohydrates. Without microbial deterioration, digested end products of proteins remain as amines, ammonia, and amino acids. Excess concentrations of ammonia have connections to developments of malignant growths tested by Hamer et al., [3].

Soluble and insoluble dietary fibers present in the food becomes the substrate for the organisms to grow, especially certain polysaccharides such as inulin, starch, and oligosaccharides upon which certain good probiotic microbes (*bifidobacteria* and *lactobacilli*) grow and produce SCFAs and prevents the other pathogenic organisms to grow. Acetates, butyrates, and propionates are the formed SCFAs in the colon region. Acetate produced is used for lipogenesis and cholesterol metabolism through HMG-CoA and also regulates the appetite inducement experimented by Frost et al., [4]. Dysbiosis is a condition where there is an imbalance in the existence of a naturally occurring organism in the host. Propionates formed, aids in gluconeogenesis in the liver by interacting with fatty acid receptors in the gut and so doing supports satiety expression [5]. Butyrate acts as a base source for human colonocytes and lays the foundation for cell apoptosis of colon cancer cells, besides inducing the gluconeogenesis of colon cells. Moreover, butyrate produced by microbes helps in maintaining the oxygen saturation in GI tract by creating hypoxia and



increases beta-oxidation of intestinal cells. Maintaining the oxygen level indirectly controls aerobic organisms and prevents dysbiosis. Microbial enzymes stimulate the production of secondary unconjugated bile acids which are involved in signaling mechanisms with gut-brain axis. Moreover, microbial enzymes are embroiled in guiding the key metabolic pathways of the human host. Quantity of production of trimethylamine from consumed meat and dairy intakes (from phosphatidylcholine and carnitine) completely based on GI organisms. This trimethylamine gets oxidized in the liver as trimethylamine-N-oxide that has a direct correlation with CVD incidence. Also, indole propionic acid by microbes from prebiotic sources has good ROS scavenging potential and helps in diabetes and obesity conditions [6]. That is why people with diabetes are prescribed high fiber diets. Microbiota part as synbiotics is more beneficial in mitigating diseases.

Microbiome and immunity

Many scientific studies show that there exists a strong relationship and communications between nutrition, metabolism, and probiotic microbiome and it may establish normal host homeostasis. If any disturbances happen in the composition and the function of the probiotic population that can lead to the development of various diseases. It also regulates the host's immune system response through specific gene activation by a localized response in the GI tract and also manipulates brain cells activities through bidirectional neuronal signaling over a part of gut-brain axis [7]. Signals from intestinal bacteria are known for priming systemic immune responses and for regulating pro- and anti-inflammatory host immune responses. Those cells that are responsible are T regulatory cells (T_{regs}) and T helper 17 (Th17) cells. A small disturbance in these interconnections predisposes inflammation and sepsis. External factors that influence the composition and function of human gut microflora are birth mode, breastfeeding, diet, exercise, disease conditions, aging, drug effects, and also geographical location [8]. Also, many internal factors that influence the gut microbiome are rapid turnover of the GI epithelium and mucus, the exposure to the peristaltic activity, the presence of metabolites from digestion, the pancreatic and biliary secretions, the host defense, the changes in pH and redox potential, and the exposure to transient organisms from the oral cavity and esophagus or any infections and its endotoxins.

Immunity is of two types, one is innate and another one is adaptive immunity. The effect of the microbiome on innate immunity can be explained by the maintenance of microbiota and immune homeostasis, innate epithelial barrier defense. Gut organisms produce microbial Toll-Like Receptors -TLR or Nod Like Receptors -NLR that are Nucleotide-Binding Domain and Leucine-Rich Repeat Containing Family. These two components have a direct effect on Peyer's patch (aggregated lymphoid nodules which act as a surveillance system of microbial populations in the gut lumen). The gut microbial products behave as a cause of microbe-associated molecular patterns (MAMPs) that bind pattern recognition receptors (PRRs) on innate cells such as monocytes/macrophages and natural killer (NK) cells, thereby releasing cytokines such as IL-1 β , IL-6, IL-12, IL-15, and IL-18 that act upon pathogenic exposure.

This sequence of responses leads to altered cellular metabolism. Thus, microbial products influence the epigenetic reprogramming and increase in responsiveness in the innate immunity GI tract. Similarly, these microbial ligands reach the bone marrow through blood circulation and influence InterLeukin-1 β and Granulocyte-Macrophage Colony Stimulating Factor receptor which controls the production and functions of blood cells. MAMPs ligands impact bone marrow hematopoietic progenitors to induce long-term memory traits. These arrangements directly or indirectly affect the metabolic reprogramming and increase the responsiveness and are held responsible for the increased glycolysis, increased cholesterol metabolism, and enhanced myelopoiesis for mounting the beneficial inflammatory response during systemic infections.

In adaptive immunity, there exists a direct and indirect resistance of the gut microbiota to colonization by the enteric pathogens. Through direct competition, the resident microorganisms directly constrain the establishment and proliferation of the incoming enteric pathogens. Commensal microorganisms present in the gut compete for the pooled nutrient such as carbohydrates, amino acids, and organic acids with pathogens. Besides, commensal bacterial strains such as *Bacteroides thetaiotaomicron* catabolize mucin to produce fucose, which hinders virulence factor expression by pathogenic *Escherichia coli*. Enteric pathogens have evolved strategies to overcome competition by commensal bacteria.



Some pathogens can directly kill their commensal competitors through their type VI secretion system (T6SS). This is a system mostly used by gram-negative bacteria for protein transport across the cellular envelope into an adjacent target cell. Pathogen-induced inflammation, which leads to increased epithelial cell turnover, provides nutrients that selectively promote the growth of pathogens. Moreover, pathogens can localize to epithelium-associated niches that are devoid of commensal bacteria and use nutrients near the epithelium to escape direct competition with resident microorganisms. Through indirect mechanisms of competition, the commensal bacteria catabolize polysaccharides to generate short-chain fatty acid (SCFAs), such as acetate, which enhances intestinal epithelial cell barrier function.

In addition, commensal microbiota promotes the production of mucus and the release of antimicrobial peptides such as regenerating islet-derived protein 3 γ (REGIII γ) from epithelial cells to restrict pathogen colonization and proliferation. Innate immune cells, such as intestinal resident macrophages, neutrophils, and some group 3 innate lymphoid cells (namely ILC3s), as well as T helper 1 (TH1) cells, TH17 cells, and IgA-producing B cells and plasma cells, are also activated by the microbiota to restrict pathogen colonization.

Impact of diet on the human gut microbiota

Dietary intakes have direct sway over the microbiome makeup of body. We can bring down dysbiosis by consuming foods that harbor beneficial microbes. Narrowing of host dietary diversity and reduced intake of essential nutrients can therefore reduce the availability of substrates for specific microbial growth and contribute to intestinal dysbiosis. When we consider the rural diet and western diets, the time of consumption of meals and the quality of food differs.

Filippo et al., [9] revealed the impact of diet in shaping gut microbiota by conducting a comparative study on children from Europe and rural Africa. African children who consumed low-fat and high-fiber diet had less pathogenic bacteria and microbial richness than European children who consumed a high-fat diet (Western diet). Especially African children had a depletion in *Firmicutes* and a greater abundance of the phylum *Bacteroidetes* (*Xylanibacter* and *Prevotella*), whereas European children showed a significant increase of *Firmicutes* (*Faecalibacterium* and *Acetivomaculum*) and Enterobacteriaceae (*Shigella* and *Escherichia*). Marlow et al., [10] validated a small reduction of the acute phase protein C-reactive protein (CRP), an increase in *Bacteroidetes* and *Clostridium* clusters, and a decrease in *Proteobacteria* and *Bacillaceae* population when they were fed with Mediterranean-inspired anti-inflammatory diet. Also, the study group who followed the Mediterranean diet had increased *Prevotella* and short-chain fatty acids.

Matijasic et al., [11] observed a high percentage of bacterial populations such as *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii*, *Bacteroidetes*, *Prevotella*, and *Clostridium clostridioforme* in people consuming omnivore diet and also found a lesser cluster of the *Clostridium XIVa* in people who regularly consume a vegan and vegetarian diet.

Vulevic et al., [12] studied the effect of a high fiber diet and found an elevation of *Bifidobacteria* and a reduction of *Bacteroides* spp. and *Clostridium histolyticum* group in a cohort of overweight adults after administration of prebiotics (GOS).

Many studies have shown that high-fat diets lead to a decrease in *Bacteroidetes* and an increase in *Firmicutes*. These effects may be associated with increased gut permeability, a higher capacity for energy harvest and storage, and inflammation [13].

An animal-based diet in humans showed an increase in the abundance of bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) and a decrease in the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*) studied by David et al., [14].

COVID-19 and cytokine storm

When there is an attack of coronavirus infection series of changes occur inside our body. The whole process is called a cytokine storm. There will be a huge rush of cytokines, a type of signaling molecule from helper T cells, and macrophages to the site of infections that induce inflammation. The rapid increase in cytokines



attracts an excess of immune cells and thus, infiltration of these cells into lung tissue and leads to lung injury. This may further lead to high fever along with excessive leakiness of blood vessels. Affected patients also have blood clotting inside the body, extremely low blood pressure, hypoxia, and acidity of the blood and finally, it may cause pleural effusion (accumulation of fluids in the lungs). Our body's natural defense system, i.e WBC attacks and inflames even the healthy tissue and organ resulting in Multiple Organ Dysfunction due to physiological derangement, and this condition further worsens the acute respiratory distress syndrome (ARDS). Those physiological derangements affect the formation of a membrane made up of dead cells and proteins (hyaline) that lines the lung and thereby, poor oxygen absorption. All these sequences end up with the possibilities of entry of other organisms, which are very similar to SARS-CoV-2 intestines. Moreover, it increases the inflammation and leakiness of the gut lining that attracts opportunistic infections by other pathogenic organisms. To improve the immune defense and functions of the intestine and to alleviate dysbiosis conditions, four important categories of food and its component are considered. They are probiotics, prebiotics, nutrients, and amino acids.

Dietary significance in COVID pandemic

The progressive increase in COVID-19 related mortality is likely the result of immunosenescence, the immune decline that occurs with age, whereby the thymus shrinks, resulting in fewer and less effective T cells in the circulation and a reduced thymus output [15]. This pandemic situation has raised reparations for consumers, restitution to producers, and restorations to policymakers worldwide. There exists a complex interrelationship between immediate physiological responses to food, the nutrition metabolism, and immune coordination of the body. From the viewpoint of microbiome make-up that has an enormous beneficial effect. Many studies correlate probiotic intakes and behavioral outcomes. Silk et al., [16] determined the efficacy of a novel prebiotic trans galactooligosaccharides in changing the colonic microflora and improve the symptoms in IBS sufferers (44 patients). They found that GOS supplementation stimulated the gut Bifidobacteria and alleviates the IBS symptoms. The consumption of probiotic yogurt improved the moods of those who were initially critical [17]. To evaluate the antidepressant potential properties of probiotics, Debonnet et al., [18] studied twenty adult male Sprague-Dawley rats chronically treated with *Bifidobacteria infantis*. Bifidobacteria suppress immune cell production and release of cytokines in response to mitogen stimulation in the peripheral circulation. Diet, nutrition and nutritional status connection with microbiome are substantial in supporting the immune system to battle against the virus. People around have inexorable questions about the food quality and its safety and scientific fraternities should have relevant answers.

Conclusion

A multi-level framework of management is necessary to maintain the dietary requirements and immune nutrition Naja and Hamedeh, [19]. At an individual level, food utilization pattern, changes in eating pattern, physical activity are needed to be modified to sustain the dietary essentials that have an immediate effect on nutrition and immunity. Parameters at the community level include management of food accessibility, availability, social support, equity among vulnerable groups that paves way for better dietary intakes among the group of people. Taking an account of national needs of nutrition amid the covid-19, food and agricultural policies, food marketing and media, food security at the national level, food assistance programs, and the healthy food basket are to be taken care of. While thinking big on nutrition and dietary patterns at the global level; food standards, food distribution and shipping, food trade agreement, research, and capacity building, commodity pricing are the impactful measures. Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism, especially macrophages functions, polarization, T cells, and B cells functions. Targeting the gut microbiome, with probiotics and other functional foods will have beneficial effects on human health in many ways. There should exist homeostasis between the human host and microbiome to have a healthy symbiosis. Fecal microbiota transplantation (FMT) is the process of administration of a solution of fecal matter from a donor into the intestinal tract of a recipient to directly change the recipient's gut microbial composition and confer a health benefit. Frequent gas or bloating, cramping, urgency, and/or mucus in feces, food sensitivities, chronic bad



breath, loose stool, diarrhea, constipation, or a combination. Irritable Bowel Syndrome (IBS), carbohydrate intolerance, particularly after eating fiber and/or beans are maybe indications of dysbiosis conditions. Possibilities of correction of dysbiotic conditions may improve human health.

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