

## Homeostatic Microbiome (Microbiota) – Formation, Maintenance and Influence on Human Health

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**Conflict-of-interest statement:** The author declares that there is no conflict of interest regarding the publication of this paper.

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Received: July 25, 2018

Revised: September 28, 2018

Accepted: September 30, 2018

Published online: December 21, 2018

### ABSTRACT

Homeostatic microbiome (HM) is one of the key factors in maintaining human health. However, HM during human life is exposed to the continuous action of external factors that can cause temporary or permanent changes. If food is considered not only as a source of nutrients, but also as a carrier of the accompanying microbiome, the question is how nutrition impacts on maintenance and changes in HM. This work follows the changes of microbiome from the birth to the old age in order to gain insight into what type of diet is the best for preserving healthy HM. Beside dietary regime,

normal functioning of HM is influenced by the four basic elements: water (type and frequency of fluid intake), air (CO<sub>2</sub>, O<sub>2</sub>, etc.), soil (mineral composition of food), fire (temperature). HM combines all of these elements, so it represents the fifth key element for human health and life as well as for the Nature.

**Key words:** Homeostatic Microbiome; Gastrointestinal microbiome; Nutrition; Actinobacteria; Firmicutes; Fifth element

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Nikolic DM. Homeostatic Microbiome (Microbiota) – Formation, Maintenance and Influence on Human Health. *Journal of Gastroenterology and Hepatology Research* 2018; **7(6)**: 2729-2733 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2471>

### INTRODUCTION

Homeostatic microbiome (HM) or microbiota is a community of microorganisms that inhabit a particular environment and especially microorganisms living in or on the human body. In interaction with other physiological systems and environment, microbiome is crucial for the maintenance of normal immunologic, hormonal and metabolic homeostasis and health of its host. Formation of the HM begins immediately after birth and continues throughout life. HM is necessary for normal function of vital physiological systems. During life HM is susceptible to great changes such as: antibiotic therapies, change of the environment (migration), dietary changes and changes in proper functioning of other physiological systems. Based on the law of connected vessels, all physiological systems are important in maintenance of homeostasis, and disorder of one system leads to disorders of other physiological systems. Maintenance of normal homeostasis provides long and healthy life. Formation of HM (ring of life) includes several important steps and phases: pregnancy and childbirth, breastfeeding, contact with family members and wider environment, nutrition and sexual contacts<sup>[1]</sup>.

Microbiome research, a new field investigating how microorganism affect human health have revealed that HM is related to diseases such as irritable bowel syndrome (IBS), Crohn's disease, malnutrition, cardiovascular disease, Alzheimer's disease, chronic

fatigue syndrome (CFS), and especially with diabetes and obesity, due to overgrowth of *Candida* and certain bacteria, which penetrate directly into pancreas causing insulin secretion disorder<sup>[2,3,4,5]</sup>.

This manuscript looks into how diet, as one of the crucial factors, impacts on formation and maintenance of HM during life.

The first step in formation of the ring of life, preceding nutrition, is the birth, i.e. contact of the newborns with mother and immediate surroundings. During birth and immediately thereafter, infants come in contact with vaginal and gastrointestinal microflora of the mother. This is the first step in colonization of intact organism, although some recent researches suggest colonization may begin even earlier. The mode of delivery (Cesarean or vaginal, CD and VD, respectively) has impact on intestinal microbiota composition in newborns and the differences may remain up to seven years after delivery. Since intestinal microbiota are very important for postnatal development of the immune system, initial colonization during CD or VD may lead to changes in full colonization thus influencing on development of the immune system and possible pathogenesis of some allergic and autoimmune diseases. There is association between CD and increased rate of asthma, especially in females, and allergic rhinitis, diabetes mellitus type 1 and celiac disease<sup>[6]</sup>.

## NUTRITION IN NEWBORNS AND ADULTS AND ITS EFFECT ON CHANGE AND MAINTENANCE OF HM DURING LIFE

### Breastfeeding

Breast milk is the first and sole source of nutrition and fundamental for adequate intestinal immune development. Breast milk contains several important nutrients and stimulates proliferation of specific microorganisms (*Bifidobacteria*, *Lactobacillus* and *Bacteroides*). Breast milk influence on primary microbiota in newborns thus preventing expression of immune-mediated diseases (asthma, inflammatory bowel disease, diabetes type 1)<sup>[7]</sup>. Human milk is also a source of commensal bacteria and the very act of breastfeeding is the source of certain microorganisms (e.g. maternal skin, oral cavity of newborns exposed to the mother's vaginal and intestinal microbiota during childbirth). More than 700 species of bacteria are present in colostrum and mature milk<sup>[8]</sup>.

### Nutrition from birth to 3 years of age

Contact with microbes from environment is crucial since it is period when immune system is learning to recognize its own antigens from external ones. The question is how immune system distinguishes good bacteria from bad ones. Probably there is no such mechanism, but immune system reacts only in case of HM disorders, due to overgrowth of certain microorganisms which pass from commensal into the pathogens. Human body comes to contact with environmental microorganisms primarily through food and then through immediate environment (air, water, body contact). Nutrition in the first years of life is very important for tolerance formation against certain antigens from environment.

It is assumed that distal part of small intestine and rectum are first colonized by facultative anaerobic bacteria including *Staphylococcus*, *Streptococcus*, *Escherichia coli* and *Enterobacteria*. These are later replaced by facultative anaerobes which dominate gastrointestinal tract, primarily Actinobacteria (*Bifidobacterium* species, specifically, *B. breve*, *B. longum*, *B. dentium*, *B. infantis*, and *B. pseudocatenulatum*) and Firmicutes (*Lactobacillus*, *Enterococcus* and *Clostridium* species)<sup>[9]</sup>.

With introduction of solid foods, gut microbiome composition is changing – some bacterial species decline (*Bifidobacterium*, *Lactobacillus* species and Enterobacteriaceae), some are increased (*Bacteroidetes*) because they are necessary for the breakdown of complex plant polysaccharides. Around the age of 3 years old, a stable gut microbiome is formed.

### Influence of dietary regimes ,antibiotic treatments and age on the adult microbiome

Typical adult intestinal microbiome consist of six or seven different bacterial phyla, particularly Bacteroidetes and Firmicutes . However, during life microbiome of a person is changing and is directly correlated with the type of diet<sup>[10]</sup>.

The composition of human adult microbiome is individual-specific, so there is not one uniform microbiome. The importance of stable HM is shown by fact that upon ageing, stability and diversity of microorganism decline with health deterioration. However, if health remains intact, microbiome composition retains stability and structure as in young adults<sup>[11]</sup>.

Claesson *et al* (2012) have determined that elderly community residents have more diverse individual microbiota than one living in long-term care objects thanks to healthier and more versatile diet. I agree that diet impacts on microbiome composition, but in my opinion, mutual contact between elderly inside the centers, which represent a special ecological niche, is greater. Older people living in community have diverse contact with other persons and environment. Direct contact with persons from wider community with different HM and with microbiome from wider ecological niche is very important to preserve HM<sup>[11]</sup>.

The use of broad-spectrum antibiotics in elderly populations leads to overgrowth of *Clostridium difficile*, often resulting in a life threatening infection. Antibiotic treatment cause decline in commensal anaerobes (*Bacteroides*, *Lactobacillus* and *Bifidobacterium*) and a rise in proteolytic and pathogenic bacteria (*Fusobacteria*, *Propionibacteria*, *Clostridia*, and *E. coli*)<sup>[12]</sup>.

Effects of antibiotic use on HM depend on the type and the doses. A study by Bartosch *et al* (2004) revealed that the same antibiotic, clarithromycin, had different effects at different doses. A low dose of the antibiotic decreased the proportion of Bacteroidetes (*Bacteroides* and *Parabacteroides*) and increased Firmicutes (*Alistipes*) while high dose had the opposite effect, increased the proportion of Bacteroidetes (*Parabacteroides*) and decreased the proportion of Firmicutes (*Alistipes*)<sup>[13]</sup>.

It is common to give patients antibiotics with probiotics. In my opinion it is a wrong approach, since broad-spectrum antibiotics affect development of bacteria in probiotics. It is better to use probiotics after antibiotic therapy. In case when antibiotic treatment is no longer than seven days, saprophyte flora will regenerate on its own with regular diet. The question is what long-term effect probiotics have, harmful or beneficial. *Lactobacillus* and *Bifidobacterium* are often reduced in older people due to health deterioration.

## FOOD AS CARRIER OF SPECIFIC MICROBIOTA

Consumption of food from environment in the early stage of growing up is essential for formation of normal HM. But nowadays, HM is threatened by nutrition since naturally grown food is not consumed, but the most available canned food. Packaged food contains preservatives, which act as antibiotics or the food is sterilized. Products from farm (meat, milk, eggs, vegetables) are from animals

which are not in contact with bacteria from surrounding ecosystems. In order to prevent spreading of infections in such small space, animals are treated with antibiotics.

During cultivation of fruits and especially vegetables, artificial fertilizers and pesticides are used, seriously disrupting normal microorganism ecosystem. For example, together with organically grown (without pesticides) carrot, one will inevitably take in microorganisms from the soil also. Natural process is to consume food together with microorganisms.

Permanent healthy food intake provides regeneration of human HM. For example, after using probiotics for seven days, HM restore the initial formation. Even disrupted HM, as well as healthy HM, defends against sudden changes. It is very difficult to make good and permanent change.

Another kind of food containing a lot of microorganisms is naturally fermented fruits and vegetables. There are scientific papers dealing with this subject. But it is still to establish whether consumption of fermented food have positive or negative impact on the microbiota composition.

Fermented foods are potential source of probiotics, especially of lactic acid bacteria such as *Lactobacillus plantarum*, *L.pentosus*, *L.brevis*, *L.fermentum*, *L.casei*, *Leuconostoc mesenteroides* and *L.fallax*. Fermented fruits and vegetables contain diverse prebiotic compounds which stimulate growth of probiotics and there are numerous evidences of positive effects of probiotics on human health<sup>[14]</sup>.

There are some interesting data about diversity and specificity of microbiological flora of different fruits and vegetables grown by conventionally or organic farming.

There are diverse bacterial populations on the surfaces of fruits and vegetables and the communities on each produce type are significantly distinct from one another (Figure 1), certain produce types (i.e. sprouts, spinach, lettuce, tomatoes, peppers, and strawberries) have more similar communities with relative abundances of taxa belonging to the family Enterobacteriaceae, while other produce types (i.e., apples, peaches, grapes, and mushrooms) have predominantly taxa belonging to the Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria phyla. It is established that there are significant differences in bacterial composition between conventionally and organically-grown analogs, the latter having less abundant Enterobacteriaceae taxa<sup>[15]</sup>.

One of easily accessible food is cheese, a huge source of bacterial community which can have favorable or adverse impact on HM<sup>[16,17]</sup>.

Cheese is product whose microorganism content depends on environment where it is produced i.e. from its origin. In small production there are not two cheeses with the same microbial composition. That is why only cheeses from similar surroundings should be consummated. Consumption of cheeses from other states and region should be avoided. Given the frequent migration of the population, it is clear that change of diet, ecological niche and surrounding has a huge impact on HM composition.

The microbial diversity of raw milk cheese depends on both the milk microbiota and on traditional practices, including inoculation. Traditional processing maintains both the richness of the microbiota and the diversity between cheeses. There are more than 400 species of lactic acid bacteria, Gram and catalase-positive bacteria, Gram-negative bacteria, yeasts and moulds in raw milk. This biodiversity decreases in cheese cores, where lactic acid bacteria are numerically

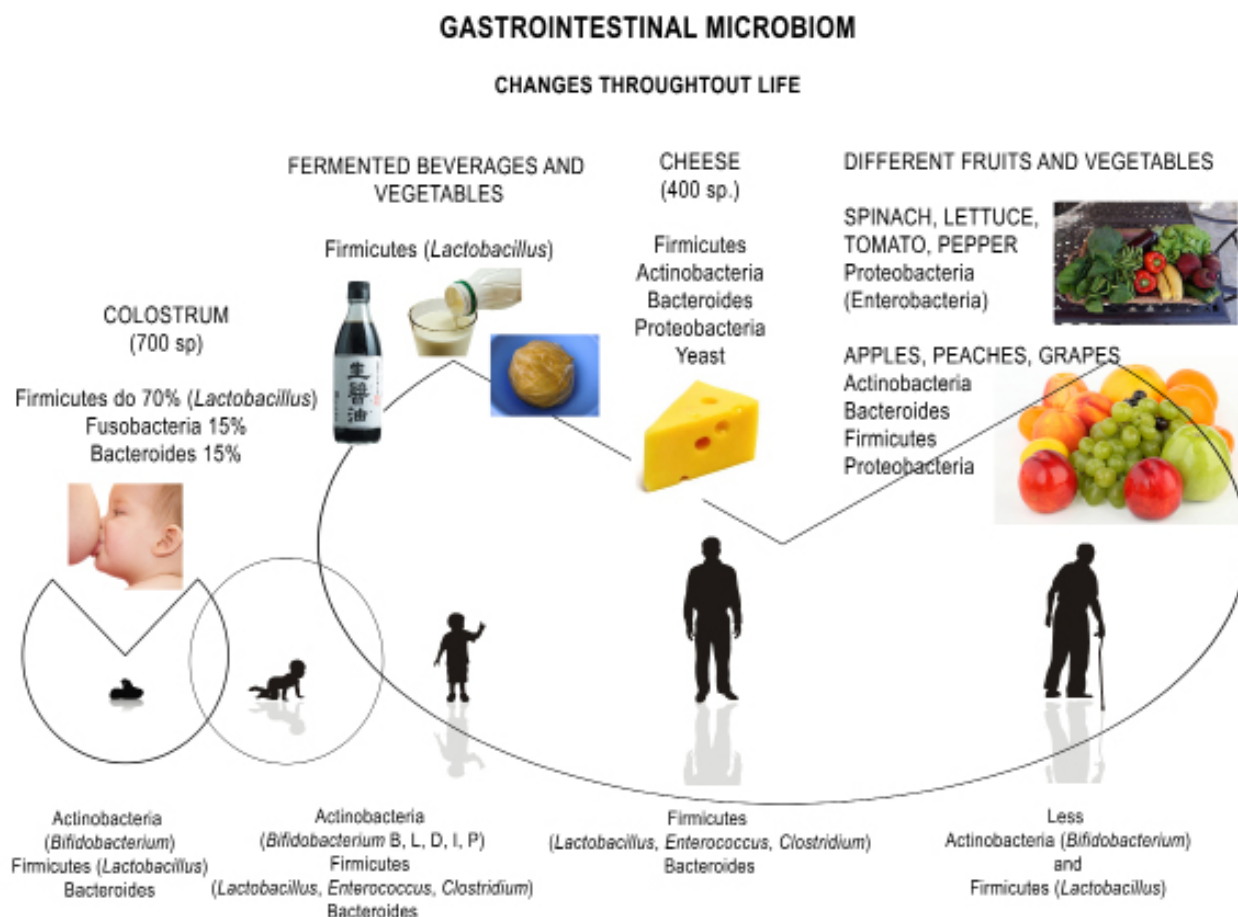


Figure 1 Relationship between gut microbiota and microbiome intake from the environment through a variety of foods.

dominant, but persists on the cheese surfaces, where numerous species of bacteria, yeasts and moulds are present. Diversity between cheeses is due particularly to wide variations in the dynamics of the same species in different cheeses. Flavour is more intense and rich in raw milk cheeses than in cheeses made from pasteurized or microfiltered milk thanks to abundant native microbiota<sup>[16]</sup>.

There is extensive Earth Microbiome Project designed to characterize the diversity, distribution, and structure of microbial ecosystems across the earth<sup>[18]</sup>. This is enormous task, resembling impossible mission, but very important link necessary for better understanding of HM.

Consumption of organic fruits, prunes and grapes, grown without pesticides, provides intake of natural probiotics thus helping maintenance of natural HM. This is valid if one has formed healthy HM which tends to keep this formation. HM is resistant to environmental factors, but also very sensitive. Nutritionists recommend diverse diet, which is partly justified, since only steady diet could lead to a stable HM. Therefore, the type of diet after birth and in early childhood should not be changed a lot. Microorganisms in the gut are the most effective in digestion of the food they are already prepared for, i.e. they are abundant enough for fast and efficient degradation of the food.

It is very important to consume the food with the microbiome present in the food because the goal of bacteria is degradation (decay) of the food. Normally, fruits and vegetables degrade with time and similar process is present in the gastrointestinal system. Consumption of raw food (fruits and tuberous crops with peel) is desirable since it is a way to intake microbiota present in the foodstuffs. Canned food is much more difficult to digest and requires more time. Since there are numerous spores in the air, it is practically impossible to consume sterile food.

Next question is what kind of food should be taken together and what not. Intake of different microbiomes could lead to their competition and intolerance in gastrointestinal tract. For example, the relationship between *Lactobacillus* sp from dairy products and microorganisms taken with meat and fats is unknown. Is it consumption of diverse food in one meal good for digestion and for stable HM? There are a lot of questions, yet we don't have adequate answers.

Harmful impact of antibiotics on HM is often mentioned. This is not quite true. Correct and not long-term use of antibiotics cannot disrupt HM permanently. Moreover, infectious conditions in humans are consequences of disrupted HM due to overgrowth of some microorganisms which became pathogenic. In such cases antibiotics reduce number of pathogens bringing HM to the equilibrium state. If it is confirmed that certain diseases are consequence of disrupted HM, than antibiotics are drugs of choice and future researches and thinking should be continued in that direction.

Microbiome researches are relating primarily to bacteria and not fungi which are insufficiently studied, but very important factor of HM. It is not known yet what harmful or favorable changes they can cause in one organism and what their relation with bacteria is.

The conclusion is that nutrition is a key factor in formation and preservation of HM, as well as cultivation method and origin of the food. There are different points of view and recommendations of nutritionists regarding chemical composition of the food (proteins, carbohydrates and lipids), but there is none for accompanying microbiota. It is a question how mixed meal, temperature, frequency and amount of the meal during one day and one week, fermented products and beverage consumption influence on HM and what is the best. The only answer is traditional nutrition thousands of years old,

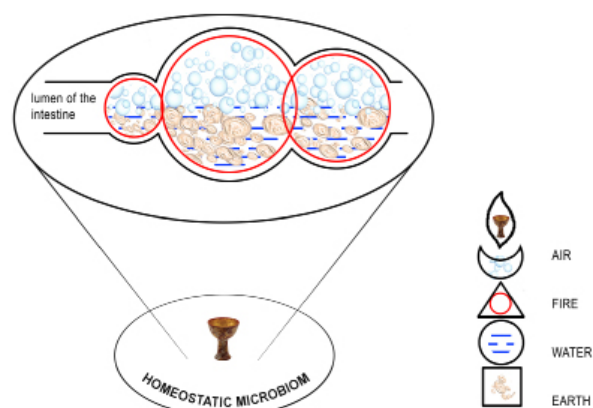


Figure 2 Homeostatic Microbiome as the fifth element.

especially among the Chinese people.

If one healthy organism is a unique microbiome carrying certain characteristics from its ecological environment and its population, what kind of changes migrations/traveling can provoke (nowadays migrations are extensive, especially in Europe) in the target population. A drastic example, with catastrophic consequences is extinction of Native Americans caused by contagious diseases brought by Europeans (American Indians have never been in the contact with this diseases before Europeans came). Nations which are trying to preserve their traditional diet (especially Oriental) regardless of their residence, do the right thing for their HM.

Another question is what changes in HM can cause mixed marriages between people of distant populations since sexual contact is also one of the major factors in intermingling of two HM. It is yet to discover are they positive or negative for one of the partners and their offspring.

If food is one of the most important factors in maintenance of human HM throughout life, then all the members of one family (younger and older) would have similar microbiota, but it is not so. This confirms the fact that HM is associated with other organic systems that change with the aging (biological clock). Time obviously influences the inevitable changes in HM.

Beside dietary regime, normal functioning of HM is influenced by the four basic elements: water (type and frequency of fluid intake), air (CO<sub>2</sub>, O<sub>2</sub>, etc.), soil (mineral composition of food), fire (temperature). HM combines all of these elements, so it represents the fifth key element for human health and life as well as for the Nature (Figure 2).

## ACKNOWLEDGMENT

This work was supported by the Ministry of Education and Science of the Republic of Serbia (Gr. No. 41002).

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