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Review Article | International Journal of Nutrition | ISSN: 2379-7835 | Freely Available Online

What is known Today about Nutrition and Microbiota

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Running title:

Nutrition in the era of the microbiota

Keywords:

Microbiota, nutrition, taste receptors, new medicine.

Received: Mar 03, 2022

Accepted: Mar 10, 2022

Published: Mar 15, 2022

DOI:
10.14302/issn.2379-7835.ijn-22-4120

Abstract

We are experiencing years of profound cultural revolution. New insights into the microbiota upset concepts in physiology, medicine, and nutrition. The role of the microbiota for our health is increasingly evident. We are increasingly certain that our health depends on that of the microbiota, or, rather, on its strength in controlling the physiology of body organs, the mechanisms of repair and protection. It is not so much a pathogen that makes us fall ill, but a reduced ability to protect and repair ourselves from damage produced by pathogens that affect us continually. Current knowledge leads us to a new medicine aimed at curing the microbiota so that it can (come back to) take care of us. In this new medicine, food rediscovers a fundamental role, since it is the best way to communicate with the microbiota, to modulate and strengthen it. And it is curious how the most recent acquisitions bring us back to the past, to an ancient medicine, which we had forgotten after the discovery of drugs, imagined capable of acting on complex pathogenetic mechanisms.

By acting, more simply, on the microbiota we can activate powerful endogenous mechanisms, which keep us healthy, when we are, more powerful than any drug we can invent. Now there is nothing left to do but apply the new knowledge.

Introduction

The knowledge about the microbiota turns upside down many aspects of nutrition.

We recently discovered that the human body is an ecosystem made up of protozoa, archaea, eukaryotes, viruses, which are 100 times our cell, and bacteria, 10 times our cell, that live symbiotically with our cellular body. In this ecosystem, the microbiota has been defined as the tip of the balance between health and disease.[1] Furthermore, our cellular body is not even at the center of this ecosystem, just as the Earth is not at the center of the Universe.[2] This diverse and complex microbiome serves as a functional expansion of host genomes, and it is estimated to harbor 50- to 100-fold more genes, compared to the host. These extra genes have added varied enzymatic proteins which were not-encoded by the host, and play a critical role in facilitating host metabolism, thus contributing to the regulation of host physiology, but, also, letting us understand the role of microbiota in food digestion.

Recent investigations are specifically related to the bacterial microbiome in the gastrointestinal tract, the largest microbial reservoir of the human body. Gut microbiota and the microbial-synthesized metabolites are discussed, along with their roles, in human wellness and normal functioning.[3] Besides controlling the physiology of all organs and vital parameters, such as blood pressure and cholesterol, it also controls the immune system and the inflammatory response: it controls our defense and repair systems.

The Role of Biodiversity of Strains in "Vulnerability in the First 1000 days" of Life and in the "Frailty of the Elder".

The most intriguing aspect is that this essential organ develops mainly in the first months of life. During fetal life we acquire only a few bacterial strains, which will then become a third of the bacterial population, even if the most characterizing: permanent symbiont, extremophile.

Within the first months of life, the bacterial population increases, as well as the biodiversity of the strains. This happens especially during weaning, where more and more complex food is introduced gradually and progressively in the diet. This process is not continuous, but in jumps, back and forth: a new food, an antibiotic, a fever or other environmental agents cause jumps that can increase or decrease the biodiversity of the strains.

Thus, mainly in the first 1000 days of life, even though weaning lasts up to 7 years, the microbiota increases the biodiversity of the strains, becoming stronger, not only towards food, but also in the control and repair processes of the human body.

The first 1000 days of life are recognized as a time of tremendous potential and enormous vulnerability, during that time stressors can produce damage whose symptoms may appear even in adulthood. As we age, we become children again. In fact, at a certain point of our life the biodiversity of bacterial strains decreases again returning towards a composition similar to the one that was as infants, producing what has been defined: "the frailty of the elderly". This is defined as the inability to repair ourselves, but also as a decreased ability in the control of our organ functions.[4] Such a frailty is responsible for enhanced vulnerability to endogenous and/or exogenous stressors and correspond to the vulnerability of the first 1000 day of life. Both are due to a low biodiversity of strains.

The Role of Food on Microbiota.

Microbiota controls inflammatory response, by which, for example, our body repairs damaged tissues, through cytokine cascade. The first cytokines intervening on damaged tissue are those named pro-inflammatory, producing necrosis, therefore they increase the damage. Then come the anti-inflammatory ones, which rebuild tissues using stem cells. In the case of low strain biodiversity different anti-inflammatory cytokines, other than those able to rebuild, are produced, while continuing

to produce the correct pro- inflammatory ones. This type of inflammatory response has been named chronic and low-grade inflammation, also named "the mother of pathologies".[5] Today the role of food in increasing the biodiversity of bacterial strains during the first phase of our life is evident as much as its role, in adulthood to delay its reduction, corresponding to our decline.

More precisely, we can understand what Hippocrates announced on the role of food as medicine: food is the best way to communicate with the microbiota and to keep it fit. Just as heavy weights are useful for strengthening muscles, complex food is also useful for maintaining adequate microbiota strength (stressors can be positive if well managed). Prolonged deprivation diets weaken the microbiota, reducing its strength not only against food, but also in the reparative processes and in the control of organs, including the immune system. By decreasing progressively the number of foods, the overall ability to process complex foods is weakened and less and less food can be managed by the digestive system (leading to food intolerance).

If we consider food as a trainer of the microbiota, we can identify what could be an optimal diet for health. [6] To be able to obtain real advantage from the use food as a medicine, we need to know how our body sees food. Current knowledge on the microbiota also disrupts this aspect. In fact, the microbiota also controls the responses of taste receptors positioned throughout the digestive system, not just on the tongue. Food allergies and intolerances depend on incorrect responses from taste receptors, not on food.

These receptors recognize and memorize the food and provide anticipatory responses to command its digestion if deemed aggressive towards the environment where most of the microbiota resides: the large intestine. They are distributed throughout the stomach, intestine, and pancreas, where they aid the digestive process by influencing appetite or satiety. We derive information from food that goes far beyond its nutritional role. It is now known that the signal molecules, e.g., leptin and ghrelin, which control appetite and satiety, are controlled by the microbiota, through the taste receptors. [7]

A better understanding of what they do and how they work could have implications for treating conditions ranging from allergy to diabetes.

These receptors recognize five flavors: sweet, sour, savory, bitter and tasty (umami), and their role is to provide a powerful safeguard against the risk of consuming potentially dangerous foods. In fact, similar taste receptors in the upper airways activate the bronchial cilia to expel the smoke if they recognize the bitter taste of nicotine or quinine, helping to clear the airways of irritating compounds, preventing the irritant from being inhaled deep into the lungs. Their response can lead us to stop breathing, cough or sneeze.

Similarly, some bitter foods cause a very rapid response - nausea and / or vomiting. Therefore, it is evident how the digestive system main role is not to nourish us, but to protect the microbiota.

It is also evident that taste receptors do not recognize food based on whether it is fat, protein or carbohydrate, but based on its taste.

In the stomach, sweet taste receptors secrete ghrelin, increasing metabolism,[8] thus encouraging the consumption of nutrients that are considered important. While in intestine the sweet receptor on L cells produce the gastrointestinal incretin hormone GLP-1, which stimulates insulin production and sends a satiety signal to the brain.[9] This "second tasting" triggers glucose transport into the cells, and the faster this happens, the more insulin will be released. It was surprising that artificial sweeteners, which were thought to influence only the tongue, also trigger changes in the gut.

Therefore, the behavioral response to carbohydrates is very different between those with a high or low glycemic index. High-glycemic carbohydrates will only stimulate appetite, not satiety.

In response to bitter food, the bitter taste receptors initially secrete ghrelin, favoring its consumption, but, after 30 minutes, decreases gastric emptying. By keeping food in the stomach, a sense of

satiety is produced. This curbs the appetite by prolonging the sense of fullness and satiety perhaps to prevent the ingestion of toxic food. This response was already known to the ancient Romans who drank wine infused with bitter herbs to stimulate appetite and prevent overeating.[10]

There can be no general rule for fats either: in fact, among fats there are noxious and healthy ones. Contrary to past dietary advice promoting low-fat diets, newer research shows that healthy fats are necessary and beneficial for health. It doesn't just depend on the fact that fats are often replaced with carbohydrates. Despite the generalized war on fat, study results show that there is no link between overall fat percentage and any important health outcomes, including cancer, heart disease and weight gain.[11, 12] Rather than adopting a low-fat diet, it!s more important to focus on eating beneficial good fats and avoiding harmful bad fats. Choose good unsaturated fats and middle and short chain saturated fats (SCFAs), limit long-chain fat saturated, and avoid bad trans fat.

Related to polyunsaturated fatty acids, Omega-6 (n-6) polyunsaturated fatty acids (PUFA) (e.g., arachidonic acid (AA)) and omega-3 (n-3) PUFA (e.g., eicosapentaenoic acid (EPA)) are precursors to potent lipid mediator signaling molecules, termed "eicosanoids," which have important roles in the regulation of inflammation. In general, eicosanoids derived from n-6 PUFA are pro-inflammatory while eicosanoids derived from n-3 PUFA are anti-inflammatory. Some medical research suggests that excessive levels of omega-6 fatty acids from seed oils relative to certain omega-3 fatty acids may increase the probability of a number of diseases.[13,14,15] A high proportion of omega-6 to omega-3 fat in the diet shifts the physiological state in the tissues toward the pathogenesis of many diseases: pro-thrombotic, pro-inflammatory, and pro- constrictive. Nowadays there is therefore a need to limit the intake of omega-6 by avoiding the use of any type of seed oil (sunflower, corn, soybean, etc.), and to increase the intake of omega-3.

Even among saturated fats, some distinction needs to be made. In fact, the general rule that saturated fats should be avoided as much as possible, makes no sense for SCFAs and medium chain triglyceride (MCTs). There is now an abundance of evidence to show that SCFAs play an important role in the maintenance of health and the development of disease. SCFAs are a subset of fatty acids that are produced by the gut microbiota during the fermentation of partially and non-digestible polysaccharides, and constitute the main nutrients of the colonocytes.[16]

Today we understand that the most important role of the digestive system is to digest aggressive food to protect the intestinal microbiota, therefore this protective action can only be carried out if the cells of this system are well nourished so that they can produce everything they need to digest food and to protect our tissues from the aggressive environment of the digestive tract. Feeding the cells of the digestive system allows to maintain a comfortable environment for the intestinal microbiota, allowing it to biodiversify its strains. SCFAs are also histone deacetylase inhibitors (HDACs), the molecules that inhibit this enzyme are used as anti-inflammatory drugs in various pathologies.[17]

The action on inflammatory processes by SCFAs is confirmed by the fact that a class of non-steroidal anti-inflammatory drugs (NSAIDs) are synthesis derivatives of acetic and propionic acid, demonstrating a contribution of their inhibition on HDAC other than on COX-2. Curiously, the inhibitory action on HADC of butyric acid is higher of all.[18] Furthermore, valproic acid, one of the most broad spectrum drugs, has been obtained by synthesis from valeric acid. SCFAs play an important role in maintaining intestinal and immune homeostasis.

The use of butyric acid was proposed as an alternative approach in autoimmune and inflammatory diseases,[19,20] against bacterial infections,[21] to reduce cell proliferation in colon cancer,[22] to reduce blood sugar, insulin resistance, dyslipidemia and gluconogenesis comparable to metformin. [23, 24, 25] Butyric acid shows protective action in experimental models of spinal muscular atrophy, [26] as well as reduces aging muscle atrophy, [27] has a therapeutic action on allergic rhinitis,[28] improves cardiac functions,[29] reduces the

intake of alcohol in dependent animals,[30] protects against severe, distant, acute lung injury caused by burns.[31]All these actions are now easily correlated to a its modulating action of inflammation. [32, 33]

Today it is no longer surprising that this intestinal action can be matched by brain actions, such as behavioral improvements in depressive anxiety states,[34, 35] in cognitive functions,[36, 37, 38] in stress responses, [39] reduction of autistic behaviors,[40,41] of manic psychosis[42], and epileptic seizures (better than valproic acid in mice with intestinal inflammation).[43]

Given that butyric acid cerebral uptake was measured in the order of 0.006%,[44] it is clear that in order to influence brain processes it does not necessarily have to enter the brain, but can act on the peripheral nervous system and the immune system.

Diets Based on the Calculation of Calories and on Simple Percent between Fats, Carbohydrates and Proteins. Do they Make Sense?

Even before the new knowledge on the microbiota, it was anachronistic to draw up diets based on the calculation of calories. In fact, the food calorie measures the amount of heat emitted by a gram of food when burned, but human body is not a stove that burn food. Food calories are calculated assuming that we get energy from food and that calorie is a unit of measurement of energy.

The misunderstanding arises from an incorrect interpretation between the energy possessed by a body and how much of it we can obtain.

The energy possessed by a body of mass m, whether it is also a food, is E = mc2, but most of this energy is not accessible and it is the same for all foods.. We can only obtain energy from differences in energy levels between, for example, the reactants and the products of a reaction. Even in violent nuclear reactions, the energy emitted corresponds to the difference in the binding energy of the nucleons between the atoms undergoing fusion or fission and the products of the nuclear reaction, just crumbs of total energy. The most common exothermic chemical reactions are those of combustion with oxygen, often used to obtain heat. For this type of reactions, it has been found useful to introduce a specific unit of measure, Kilo calorie (1 Kcal= 4184 J) defining the amount of energy emitted as heat by a unit of weight or volume of a fuel, if burned. This unit of measure allows an easier comparison of the specific heating values of the different fuels.

Therefore, food calories can be very useful for using food as fuel in a stove, but completely useless to evaluate the benefits that can derive from them, when ingested.

The new knowledge on the microbiota also makes the definition of a diet anachronistic on the basis of simple percentages of fats, carbohydrates and proteins, without indicating which ones must be chosen in each class.

Surely the work of the nutritionist becomes more complicated, having to rely more on an anamnestic data collection of the patient and less on the many commercial software for calculating diets, but, by calculating a diet on the basis of the real responses of the microbiota to food, it will be possible get better and longer lasting results.

Are the Causes of the Diet Failure due to the Patient or the Nutritionist?

Very often the patient shows a high resistance to modify the diet according to the indications provided by the nutritionist. Or rather, he manages to force the new diet for a while, but then he gives up and everything returns as it was before or even worse than before. The failure of the diet is often attributed to the patient's inability to follow it for a long period of time, but, instead, it is the fault of the nutritionist, who has not considered how the microbiota can oppose the attempt to modify it through the diet, being the microbiota itself that determines which food we should eat. We eat the food that the microbiota asks us to eat. These requests act on the deep emotional centers of the brain, food and sex are fundamental for the survival of the species, therefore it is really difficult to resist to these requests. The more drastic the change in diet, the more it happens suddenly and the sooner the microbiota will go into counterattack, restoring

what it was before or worse. It may even allow us to win some battles, but then it wins the war.

For example, Bacteroidetes prefer some fats, Bifidobacteria, fiber and Prevotella, carbohydrates.[45] A dysbiosis that leads to an increase in prevotella strain will produce a strong desire to eat sweets, which can only be reduced if this "gluttonous" strain can be reduced. In fact, since the microbiota controls the metabolism, the chocolate is differently metabolized in chocolate in different or chocolate desidering people. The urinary chocolate metabolite ratio are different in the two group of people. [46] These deep-rooted connections between the senses and the brain can make it hard to change dietary habits. Junk foods and sweet drinks are often described as addictive. It!s not a classic chemical addiction, where a single drug hits a single receptor, but a widespread activation of eager taste receptors supercharging a powerful brain response.

Only by acting on the microbiota can we change our eating habits and our way of transforming food into energy.

These actions must be aimed at modifying the environment where most of the microbiota lives. Only by modifying the environment is it possible to control the ratio between the different bacterial strains.

Conclusion

Knowledge about the microbiota has revolutionized physiology, medicine and nutrition. This microbial organ represents our control unit: human health depends on its strength and food is the best way to communicate with it.

Mainly through food we increase its strength during weaning and we can keep it strong in adulthood, delaying the physiological decline in the elderly. Today we understand that health depends on the microbiota strength to repair the damages we continually suffer and that falling ill means that these mechanisms are weak. The sickness does not depend so much on the strength of the pathogens, as on the weakness of the reparative systems.

These revolutionary concepts take us back in time, 2300 years ago, Hippocrates argued that all pathologies originate in the intestine. Hippocrates comes to define what we now know to be the actions of the microbiota: “vital force tending by nature to rebalance the disharmonies that bring pathologies” and the best medicine “consist in merely stimulating this innate force.

Now that we are starting to polish the mechanisms by which food can be the best medicine, we must deal with our mental resistances which lead to the common opinion that only a drug can be capable of healing. But these opinions, today, are not based on current scientific evidence.

According to Hippocrates:

“There are only two things: science and opinion: The first generates knowledge, the second ignorance.”

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