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Editorial
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Effects of Paleo Diet on Microbiota and Correlated Diseases

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Editorial

A healthy and balanced diet is essential to maintain a correct and healthy lifestyle and also to achieve mental health. The intake of finished products has greatly increased, together with the consumption of new chemical compounds, and new forms of nutrition, as vegetarian and vegan diets, low-carbohydrate and low-fat diets, Gluten-Free Diet (GFD) or Paleo diet without cereals, are very trendy. While it is assumed that these "elimination diets" are healthier, there are no studies confirming their effect on healthy individuals. On the contrary, several studies have shown that subject's healthy people using elimination diets are at greater risk of malnutrition, including deficiencies in minerals and vitamins. More recent studies have highlighted the gut-host interaction. A dysbiosis can be caused by infections, antibiotics, genetics and environmental changes, such as special diets. New food trends include the Paleolithic diet, promoted all over the world to improve the health of the intestine, recommends consuming lean meat, fish, vegetables, fruit and berries and avoiding the intake of cereals, legumes, dairy products, processed foods, added sugars and salt. Several studies indicate that long-term adhesion is associated with changes in the intestinal microbiota, also with possible negative impact in terms of heart health.

A healthy and balanced diet is the basis for a healthy life and well-being. In the last century, westernized communities have seen dramatic changes in the physiological and psychological relationship with food [1]. On the one hand, the availment of finished products has enormously increased, together with the consumption of new chemical compounds present in the nutritional formulation. For example, a variety of additives, including preservatives, emulsifiers, dyes and flavor enhancers, are now commonly used in the food industry and the sourdough is mainly replaced by the fermentation of yeasts. Nowadays have got popularity new kinds of nutrition, as vegetarian and vegan diets, low-carbohydrate and low-fat diets, Gluten-Free Diet (GFD) or Paleo diet without cereals. While it is assumed that these "elimination diets" are healthier, there are no studies confirming their effect on healthy individuals. On the contrary, several studies have shown that subject's healthy people using elimination diets are at greater risk of malnutrition, including deficiencies in minerals and vitamins [2]. More recent studies have highlighted the gut-host interaction [3,4]. The intestinal immune system plays a fundamental role in host defense protecting it from the harmful action of microorganisms. If this system collapses, there would be a risk of immune-mediated diseases such as autoimmune diseases. Several studies in the literature have shown that the microbiota represents a complex and balanced intestinal ecosystem that influences intestinal homeostasis and provides valuable food metabolites, such as vitamins and short-chain fatty acids, which are useful energy sources for the host. However, the gut microbiota may also be a potential causative agent of numerous associated intestinal disorders food intolerance. An increasing number of tests indicate that intestinal microbiota dysbiosis, for example, the microbial quantitative imbalance or alteration of the composition, is strongly associated with IBS, food intolerance, obesity, Crohn's disease and other inflammatory intestinal diseases [5-7]. The human intestinal microbiota hosts beneficial bacteria belongs mainly to the Firmicutes and the Bacteroides of the phylum. Obese individuals have showed reduced proportions of Bacteroides accompanied by increased levels of Firmicutes, and low-calorie diets caused a significant increase in Bacteroides. The exact mechanism by which the microbiota influences or promotes obesity is still unknown [7]. Bäckhed et al. they said that germ-free mice are protected from diet-induced obesity by mechanisms that lead to an increase

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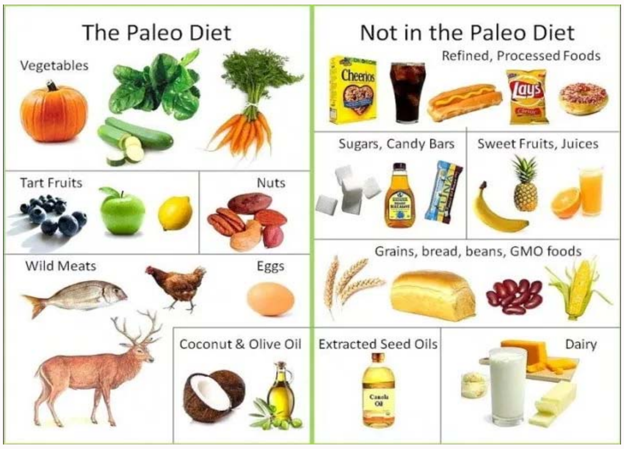

Figure 1: Paleo diet.

in fatty acid metabolism [8]. A dysbiotic condition can be caused by infections, antibiotics, genetics and the environment changes, but also specific diets. Some studies on the efficacy of the fecal microbiota, effective in *C. difficile* infection in 98% of cases, have identified dysbiosis as a symptom rather than a trigger [9]. This largely supports a potential causal role of the gut microbiota in other intestinal disorders. Several studies have shown that changes in food intake have significantly altered the gut microbiota. In fact, the availability of different types of foods favors the selective enrichment of microorganisms capable of exploiting these nutrients and supports metabolic-microbial cross-feeding, leading to the maintenance of a varied and balanced community. Even short-term changes in diet have been shown to significantly alter the structure of the gut microbiota [10]. New food trends include the Paleo diet, which is free of all cereals [11] (Figure 1). Supporters of this diet underline how, especially gluten, but also gluten-free cereals, were absent in the diet of ancient hunters and gatherers. It is believed, in fact, that the use of cereals in the human diet began in tandem with the birth of agricultural practice, about 10,000 years ago but that there has been no adjustment of the human intestine or microbiota to this drastic dietary change, although this topic is still controversially debated. Recent analyzes of the fecal metabolism of Hadza hunter-gatherers from Tanzania, which should reflect our ancient intestinal microbiota before the inclusion of gluten, have clearly shown the main differences in the microbial model and intestinal metabolites compared to Italians living in urban areas. Stool samples from Hadza hunters were collected during the rainy season, when the dominant food is plant-based (with tubers, baobabs and honey), and game meat is rare [12]. Most tubers contain a high content of moisture and indigestible fibers; therefore the Hadza diet is enriched with monosaccharide's, starch and proteins, but low in fat. The nutrition of the Italian comparison group has been adapted to the Mediterranean diet, with an abundance of vegetable foods, fresh fruit, pasta, bread and olive oil and moderate quantities of dairy products and meat. Only a small part of carbohydrates comes from fiber. Hadza's gut microbiota shows greater microbial wealth and biodiversity than the microbiota of Italian controls. Hadza's microbiota is dominated by phylum Firmicutes (72%), Bacteroides (17%), Proteobacteria (6%) and Spirochaetes (3%). The high proportions of Proteobacteria and Spirochaetes in Hadza's stool, in particular, are considerably distinct from the very low levels of these phyla in the Italian control group. The determination of the level of the genus reveals greater quantities of *Prevotella* (*Bacteroidetes*), *Treponema* (*Spirochaetes*) and *Bacteroidetes* not classified in Hadza's feces, but an absence of Bifidobacteria. The genus *Prevotella* and *Treponem* possess the degradation capacity of xylan, and the phylum Firmicutes also hosts several species that degrade the fibers. Therefore, it is suggested that these microbiotics are the prerequisite for proper digestion of the glycan and fiber-rich diet consumed by Hadza [12]. Interestingly, Hadza's feces show an unusual pattern of Clostridiales with a reduction in *Clostridium* clusters of butyrate IV and XIV production, which are considered beneficial bacteria, and the Hadza microbiota also possesses a distinct enrichment of opportunistic bacteria, for example, *Proteobacteria* or *Treponema*. In addition, the absence of *Bifidobacteria* in Hadza's gut microbiota is of particular interest because these bacteria are found in 1% to 10% of the gut microbiota of western adults and *Bifidobacteria* are considered esteemed probiotic original source agents for gastrointestinal disorders. When studying metabolic activity, there is clear evidence of the increase in the concentration of hexose in Hadza's feces compared to Italian control samples (50.5% *vs.* 16.3%). Hexoses can be enriched because the Hadza diet is dominated by polysaccharides and indigestible fibers that pass through the small intestine reach the colon and are processed by local microorganisms. There is also a surplus of sphingolipids and glycerophospholipids, but a strong depletion of amino acids and biogenic amines in the Hadza metabolome. The primitive origin of sphingolipids and glycerophospholipids in the stool is not known, since sphinges- and phospholipids are found in the phylum *Bacteroidetes* but are also naturally present in the host membranes. The metabolism of sphingolipids is further influenced by the degradation of bile, and since a typical diet rich in fiber from Hadza hunters reduces the excretion of bile acid, this can favor higher concentrations of sphingolipids. Regardless of the origin, sphingolipids and glycerophospholipids exert an anti-inflammatory effect and can be responsible for low immune stress in Hadza hunters. Interestingly, current studies have shown a high structural similarity between sphingolipids derived from bacteria and mammals and a role of bacterial sphingolipids in the maturation of the immune system has been described [13]. The Paleolithic diet, therefore, promoted all over the world to improve the health of the intestine, recommends consuming lean meat, fish, vegetables, fruit and berries and avoiding the intake of cereals, legumes, dairy products, processed foods, added sugars and salt, returning precisely, as can be deduced from the name, to a primitive diet in which we ate what was available in nature. The Australian group of Genoni A et al. [14], in a recent study, examined the impact of the paleo diet on intestinal bacteria. Precisely in relation to the growing popularity of the diet, as stated, they considered it important to understand the impact that this long-term diet could have on general health. Were recruited 44 subjects who followed the Paleolithic diet and 47 subjects (controls) who consumed a typical diet according to Australian National recommendations. The primary inclusion criteria for the Paleolithic dietary group were adherence to the dietary model for a period longer than a year and the consumption of no more than one portion per day of cereals and dairy products. For inclusion in the control group, participants did not have to make any changes to their diet in the previous year and follow a relatively healthy diet that included cereals, legumes and dairy products. The specific inclusion criteria for both groups were: men and women aged between 18 and 70; willingness to fill in a 3-day food diary (2 days a week and 1 day on a weekend), provide blood, urine and stool samples; be a non-smoker, not participate in other studies and have a body mass index <30 kg/m^2. Subjects who had taken antibiotics in the previous 6 months, had had a past or present digestive disorder, had surgery on the gastrointestinal tract, used antihypertensive or lipid-lowering drugs, had had previous cardiovascular events or diagnosed cardio-vascular diseases were excluded. Physical activity was also assessed with the administration of the "International Physical Activity Questionnaire (IPAQ)". The participants were grouped according to adherence to the Paleolithic diet, i.e. exclusion of cereals and dairy products. Two groups were created each of 22 subjects for the Paleolithic diet: Strict Paleolithic diet (RP) (consumption of less than one portion per day of cereals and dairy products) and Pseudo-Paleolithic (PP) (consumption greater than one portion per day of cereals or dairy products). The precise objective of the study was to determine the association between food intake, colon health markers, microbiota and Trimethylamine-N-Serum Oxide (TMAO), a metabolite derived from the intestine associated with cardiovascular disease. The result showed that the resistant starch inked (fraction of the starch that resists the digestive processes of the small intestine and reaches the colon where it can ferment) was lower in both groups adhering to the Paleolithic diet compared to the controls. A different composition of the microbiota with greater abundance of *Hungatella* (bacterial species that determines an increase in the concentration of TMAO) has been highlighted in the RP and PP groups, to the detriment of other bacterial species beneficial for intestinal health. Serum TMAO levels were higher in subjects who followed the Paleo diet rigorously than in Pseudopaleo and control cases, and were inversely associated with cereal intake. In addition, followers of the Paleo diet consumed twice the saturated fat. Although Paleo diet is promoted to improve intestinal health, the results indicate that long-term adhesion is associated with changes in the intestinal microbiota and the increase in TMAO, with possible negative impact in terms of heart health. A variety of fibers, including those derived from whole grains, may therefore be required to maintain healthy bowels and cardiovascular health. The populations of beneficial bacterial species were lower in the Paleolithic groups: Associated with the reduction of carbohydrate intake, this could have consequences for other long-term chronic diseases. It is known that a decrease in the relative abundance of *Bifidobacterium* has been associated with irritable bowel syndrome, obesity and inflammatory bowel disease. In addition, the Paleo diet includes a greater number of servings per day of red meat, which provides the precursor compounds for the production of TMAO and the followers of the Paleo diet have consumed twice the recommended level of saturated fat, which is also a cause for concern. Therefore the TMAO was high both due to the greater supply of red meat and to the lack of intake of whole grains with consequent modification of the intestinal microbiome. With the exclusion of all cereals, whole meal, an important source of resistant starch and many other fermentable fibers that are vital for the health of the intestinal microbiome, are also excluded. The cross-sectional data collected suggest that long-term adherence to the Paleolithic diet may not be beneficial for the health of the intestine. However, further studies are needed to clarify the impact of a Paleo diet on the gut microbiota and health outcomes in the context of western genetic and environmental conditions.

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