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KETOGENIC DIET AND INTESTINAL MICROBIOTA

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Abstract

Recent studies suggest that increased reliance on ketogenic diet offers advantages in many diseases and more recently, also as a therapy in weight loss. However, at the same time, although the research is constantly updated, the relationship between the ketogenic diet and intestinal microbiota is still controversial. In literature, in fact, there are not many experimental studies that examine the relationship between them and the effects of this diet on microbiotic level. The aim of this article is to collect and summarized the studied carried out until now in order to determine the effects evoked from the application of a KD on the intestinal microbiota.

Keywords: *ketogenic diet, microbiota.*

Introduction

The human microbiota is defined as the set of microorganism that physiologically, or sometimes pathologically, live in symbiosis with the human body.

The human microbiota is defined as the set of microorganism that physiologically, or sometimes pathologically, live in symbiosis with the human body. This microbial population is mainly concentrated in the intestinal tract and it belongs to three fundamental domains: Batteria, Archea and Eukarya present at gastrointestinal level. This microbial population has evolved for millions of years to establish an extremely advantageous symbiotic relationship for both.

Approximately 2171 species have been identified, isolated from humans, and classified into different phyla, in which the dominant are the Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia, with the two phyla Firmicutes and Bacteroidetes representing 90% of the microbiota intestinal. [1] The numerical estimate of the microorganisms present is around ten times greater than the number of human cells and more than one hundred times the amount of genomic content compared to the human genome. [2] the balance of the community is fundamental in maintaining the health of the guest and its presence brings numerous benefits: it supplies nutrients, protects against pathogens, ensures a correct function of the immune system and helps to maintain intact the barrier of intestinal mucosa. [3] So, the microbiota has structural, protective but also metabolic functions that allow the acquisition of nutrients as they favor both the biosynthesis of some substances, and the digestion and absorption of others (such as vitamin K and MAC or "undigested carbohydrates", thanks to the presence of specific enzymes).[4]

In fact, it is not surprising to observe how a condition known as dysbiosis, as well as a microbial imbalance, can lead to a series of pathological states ranging from chronic gastrointestinal diseases to disorders of neurological development. [5] [6] The composition of the microbiota is modulated by environmental factors and perhaps also by genetic factors. [3] The factors that can change the composition and, therefore, the physiology of the microbial population on (even at the level of gene expression of the human intestinal microbiome) include the geographical location, smoking, depression, living conditions (whether urban or rural), xenobiotic factors, such as the same antibiotic therapies and, finally, even the diet. [7] [8] In fact some nutrients can promote enrichment both in terms of quantity and quality, varying the structure and function of the population within the host.

It has been emphasized as diet plans, composed of unrefined foods and with a high content of "carbohydrates accessible to microbiota" known as MAC, represented by the "indigested" carbohydrates of the plant cell walls, cellulose, hemicellulose, pectins and resistant starch [9], are able to support the growth of microorganisms capable of producing short chain fatty acids, the SCFA. This is because the bacterial genome has coded over time, numerous highly specific enzymes able to digest and ferment complex macromolecules hydrolysing the glycosidic bonds. The production of these fatty acids is an important source of energy for both human colonocytes and the key signaling molecules between microbiota and host. [10] On the other hand, a diet rich in fat, low in fiber and rich in sugar determines not only a decrease in the production of SCAFA but, consequently, also a production of harmful metabolites that increase the bacterial populations most associated with inflammation chronic. [11] In the case of dietary regimes adopted as treatments for some diseases, such as the Low FODMAPS diet, for irritable bowel syndrome, and the ketogenic diet, for refractory epilepsy (but not only), they should be studied for their influence on the human microbiota; as they reduce or completely exclude certain foods, these can influence the composition of the microbiota and consequently also the physiology of the host itself. [10] [12].

Ketogenic Diet (KD)

The ketogenic diet or VLCKD (Very Low Carbohydrate Ketogenic Diet) represents a nutritional protocol characterized by a reduction in energy intake, similar to a low-calorie diet (VLCD),

but with a relative increase in protein and lipid content, resulting in an important glucose reduction, less than 50 g per day. (See the characteristics in table 1) [13]

Very Low Carbohydrate Ketogenic Diet (VLCKD)
Caloric Intake ≤ 800 Kcal
Protein Intake 0.8-1.5 Kcal/Kg p.c.
Glucidic Intake < 50 g/day (the range to induce ketogenesis), however < 1g/Kg p.c.ideal/day
Lipid Intake: Carbohydrate + Protein exected in the ratio 4:1, 3:1; 2:1.
Use of vegetables with low carbohydrate
Use of supplementes for K and Na (Bicarbonates 1.5-2 g/day), Mg, Ca, PUFA3 (1g/die) and highwater supply.

Table 1.

This nutritional protocol took its first steps and was used for the first time since the 1920s in the treatment of refractory epilepsy. [14] In fact it is a nutritional approach that is not to be considered a model of balanced diet, as can be a Mediterranean one [15], but rather as a real therapy. Current literature data have shown therapeutic evidence in the treatment of pathological states such as obesity, improvement of the indexes linked to cardiovascular risk, in the treatment of type 2 diabetes and in the treatment of refractory epilepsy. [16] In addition, preliminary data would seem to show perspectives in the treatment of acne, [17] of neurodegenerative diseases (eg autism spectrum disorders, Alzhaimer disease, Parkinson's disease, amyotrophic lateral sclerosis, Brain cancer) and in polycystic ovary syndrome. [18]

It is the biochemical principle of ketosis to give KD the great success. In fact, at a physiological level, the ketogenic diet shares several common pathways to the state of fasting; since after several days of glucidic restriction, glucose is insufficient both for fat oxidation and to guarantee the energy necessary for the central nervous system. Hence, the body begins to use ketone bodies (ß-hydroxybutyrate, acetate and acetoacetate), through the process of ketogenesis that occurs, especially at the mitochondrial level, in liver cells, as a primary fuel source. [19]

What are the effects of KD on microbiota?

We find several studies carried out both on mice and on small human samples, with the attempt to associate the application of the ketogenic diet with the modification of the intestinal microbial composition and to evaluate its effect on different pathological states. This study was created with the aim of evaluating how the ketogenic diet has altered the intestinal microbiota and improved neurovascular functions, thus reducing the risk of neurodegeneration in young healthy mice (12-14 weeks). [20] The data showed that KD therapy, applied early, therefore in the initial phase of the disease, can bring improvements both for the cerebral vascular function and to increase the beneficial intestinal microbiota, improving at the same time the metabolic profile and reducing the risk of disease of Alzheimer (AD). In this case the KD composed of short fatty acids SFA, monounsaturated fatty acids MUFA and polyunsaturated PUFA, was administered for 16 weeks to both healthy and diseased mice and numerous benefits emerged that appear to be associated with the modification of the composition of the intestinal microbiota; in particular, an increase in anti-inflammatory bacteria (Akkermansia Muciniphila and Lactobacillus) has been noted, which have the ability to generate SCFA of short-chain fatty acids, in contrast to a reduction in proinflammatory microbes (Desulfovibrio and Turicibacter). [10] This nutritional protocol, however, has reduced the overall microbial diversity due to the low content of carbohydrates (complexes), as for some microorganisms it is fundamental for their sustenance in energy metabolic terms. [21]

Another interesting study [22] was that in which the ketogenic diet was applied as a therapy for autism spectrum syndrome (ASD). The study was conducted for 10-14 days on autistic murine models, in order to assess whether the autistic symptoms found benefit and an improvement in the Firmicutes and bacteroides ratio (with reduction of Firmicutes)

which consequently determined precisely an improvement in behavioral symptoms in ASD. Many researchers study have concluded that the diet had an "antimicrobial" effect by decreasing the overall richness of microorganisms.

Other research, on the other hand, has shown that it may be a connection between microbiota and refractory epilepsy. [23] It involved two groups: one with children with refractory epilepsy (N. 14) and one with healthy newborns (N. 30). The first group before starting a KD, showed a condition of microbial imbalance with an increase in pathogenic bacteria, while subsequently, after treatment, they significantly decreased with an increase in Bacteroides spp. This happened in both groups. This effect would seem to be associated with a decrease in the convulsive effects on epileptic patients since the increase in Bacteroides spp is closely related to the digestion and metabolism of high-fat nutrients and to the regulation of the secretion of interleukins (IL) in dendritic cells, related to seizure effects on epileptic patients. The researchers therefore suggest that a KD can reduce these symptoms, leading to changes in the microbial profile of individuals.

Moreover, in a pilot study [24] conducted on 6 patients with GLUT1 DS who were asked to collect faecal samples before and after three months of the KD diet. The analyzes carried out showed that there were no statistically significant differences at 3 months in Firmicutes and Bacteroidetes. However, fecal microbial profiles revealed a statistically significant increase in Desulfovibrio spp, a bacterial group that should be involved in the acute inflammatory condition of the intestinal mucosa associated with the consumption of animal fats. The same authors actually suggest, in case of dysbiosis, the importance of an adequate integration with pre or probiotics.

CONCLUSION

Studies show that the KD diet determines an important variation of intestinal microbial species. It should be emphasized that this change is important and in some ways decisive in the treatment of epilepsy and in the improvement of neurovascular function. However, during the application of KD, there is a decrease in some families of beneficial microorganisms such as bifidobacteria and, on the other hand, an increase in others such as Akkermansia or E. Coli. These data underline how the diet has a negative impact on the mucosa of the intestinal barrier and its immunity (Table 2). Therefore, although the protocol has positive effects with regard to some important pathological conditions, concerns areraised about long-term effects, especially on healthy subjects who adopt KD for weight loss purposes. Furthermore, in order to maximize the benefit of the diet, in the necessary cases, an integration with specific pre and probiotics or fermentable foods will be necessary. Further studies are therefore needed to investigate the role of variations during ketogenic therapy so as to better establish safer and healthier interventions for patients in the short and long term.

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Table 2. Effects of different types of diet on gut microbiota.[1]

Types of diet	Vegan/Vegetarian	Gluten-free	Ketogenic	Western	Low Fodmap	Mediterranean
Increase in bacteria	Clostridium clostridoforme F.prausnitzii Klebsiella pneumoniae Bacteroides/Prevotella B.thetaiotaomicron Bacteroidetes	Bifidobacteria Victivallaceae Clostridiaceae Enterobacteria (E.coli)	Enterobacteria (E.Coli) Desulfovibrio spp Parabacteroides Bacteroidetes Akkemansia	Ruminococcus torques Enterobacteria Bilophila Alistipes Bacteroides Akkemansia		Bifidobacteria Lactobacillus Lachnospiraceae Bacteroidetes
Decrease in bacteria	Bifidobacteria Clostridium cluster XIV Bilophila	Corobacteriaceae Vellonellaceae Ruminococcus bromii Roseburia Lactobacillus Clostridium lituseburense F.prausnitzii	Bifidobacteria Eubacterium rectale Dialister Firmicutes	Bifidobacteria Roseburia Eubacterium rectale Ruminococcus bromii Lactobacillus Prevotella	Bifidobacteria Ruminococcus gnavus Clostridium Akkemansia F.prausnitzii	Clostridium Enterobacteria

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