

Review Article

The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state

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The role of the gut microbiota in understanding the onset and development of obesity is gaining importance. Dietary strategies are the main tool employed to counteract obesity, and nowadays they are focused on a wide range of different aspects of diet and not only on calorie restriction. Additionally, diet is known to be a major factor influencing modification of the gut microbiota. Therefore the influence of both macronutrient and micronutrient content of any dietary strategy to treat obesity on gut bacterial composition should now be taken into consideration, in addition to energy restriction. This review aims to collect the available data regarding the influence of different dietary components on gut microbiota in relation to obesity and inflammatory states in humans. Although more work is needed, specific dietary factors (carbohydrate, protein and Mediterranean foods) have been shown to have an influence on the gut microbiome composition, meaning that there is an opportunity to prevent and treat obesity based on microbiota outcomes.

Key Words: obesity, nutrition, gut microbiota, dietary strategies, inflammation

INTRODUCTION

Obesity has become a major public health problem being described as the 21st century epidemic since the prevalence is expected to increase further.¹ Overweight is not only a problem of itself, but also due to the obesity-associated metabolic and mechanical disorders.^{2,3} Since obesity has a multi-causal aetiology, the treatment is complex and different factors must be taken into account to design an effective therapy. Thus, it is well known that lifestyle plays a major role in the causation of this disease.¹ The genetic make-up of an individual also plays a part.⁴ More recently the gut microbiota have been proposed as contributing to both the aetiology of obesity and accompanying metabolic related disorders (Figure 1).⁵ There have not been many human intervention trials because of methodological difficulties. However, studies do suggest that the composition of the gut microflora may influence harvesting energy from food,⁶ mucosal immunity, intestinal permeability, transit time, and systemic inflammation,⁷ which all relate to obesity. A balanced gut microbiota composition confers benefit to the host, whereas microbial imbalances are associated with metabolic and immune-mediated disorders.⁸

The composition of the bacterial ecosystem varies substantially among individuals, but it is also dynamic and susceptible to change in a single individual. A change in

dietary factors is one way the microbiota composition can be shifted.^{8,9} Therefore, the study of the influence of different dietary elements on microbiota composition variation has become an area of growing scientific interest. Indeed, a relationship between the gut microbiota and obesity is well recognized, but the mechanisms underlying these interactions remain largely uncharacterized and more studies are needed in order to establish if changes in gut microbiota are a cause rather than a consequence of obesity. In any case, the ability to manipulate the microbiota through diet should provide a route for delivering health benefits.¹⁰ This review paper aims to collect and critically order the available data regarding the influence of different dietary components on gut microbiota in relation to obesity and inflammatory states in humans. This appraisal has been focused in a careful examination (between years 2000 and 2013) of current accepted databases such as Pubmed and Cochrane following accepted criteria of search, but cannot be considered as a systematic re-

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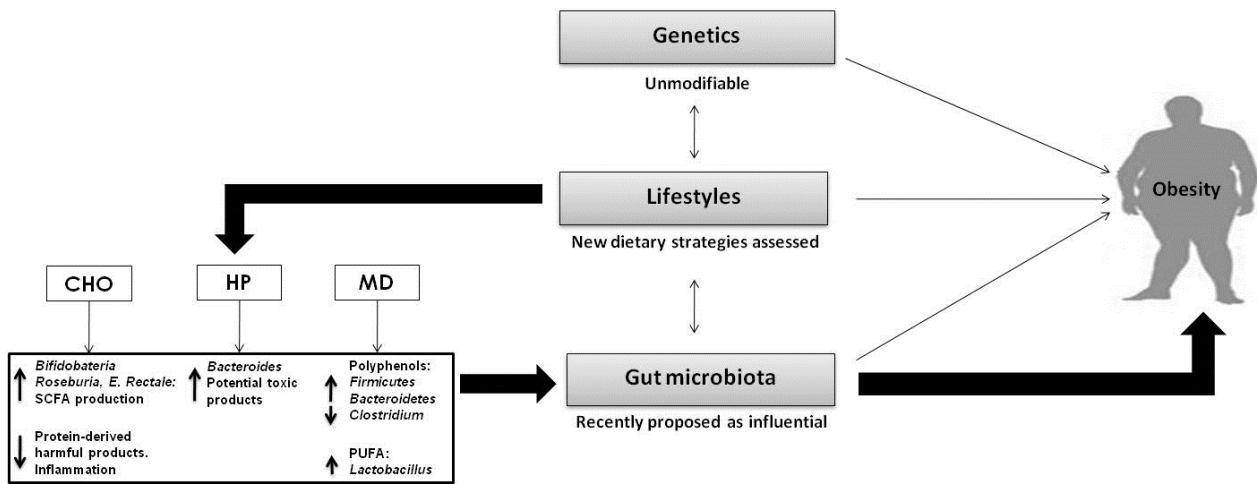


Figure 1. Interplay between genetics, lifestyles and microbiota in the obesity development. Role of specific dietary components on bacterial composition. CHO: carbohydrates; HP: high protein; MD: mediterranean diet; SCFA: short chain fatty acids; PUFA: polyunsaturated fatty acids.

view given the heterogeneity and difficulties for comparison of the available studies. The following terms “gut microbiota, carbohydrate diets, high-protein diets, Mediterranean diet” were individually screened and crossed with “nutrition, obesity, inflammation and weight loss”.

GUT MICROBIOTA

The mammalian gastrointestinal tract, particularly the large bowel, is colonized by a diverse collection of bacteria, viruses and archaea, collectively known as gut microbiota.¹¹ The gut of the fetus is sterile, but is colonized by bacteria from the mother and the environment at birth and thereafter.¹² The type of feeding and hygiene measures have also been shown to play a role in the composition of the microbiota as it colonises the gut of the newborn. The gut microbiota is estimated to consist of more than 10^4 microorganisms, with approximately 1100 prevalent species, and within any individual there are approximately 160 such species.¹³ The exact composition remains unknown, but recent investigations have shown that the majority of the bacterial phylotypes are members of two phyla: the *Firmicutes* (eg *Clostridium*, *Enterococcus*, *Lactobacillus*, *Ruminococcus*) making up 60% of the gut microbiota, and the *Bacteroidetes* (eg *Bacteroides* and *Prevotella*) making up 15%. These strains are followed by the *Actinobacteria* (eg *Bifidobacterium*) and the *Proteobacteria* (eg *Helicobacter*, *Escherichia*), as reported elsewhere.^{5,14} The bacterial diversity tends to decrease with age.¹⁵ The number of cells in the microbiota exceeds the number of human cells and contains 100 times more genes than the human genome.¹⁶

The association between the gut microflora composition and obesity was noted in observational studies, which compared germ-free mice to normal mice.¹⁷ Thus, it was observed that control animals had 42% more adipose tissue compared with germ-free ones.¹⁷ Subsequently, the microflora from normal mice was transferred to the germ-free mice and it was noted that the germ-free mice developed overweight in a period of two weeks, with an increase of 57% in their total body fat, despite no change in energy consumption or energy expenditure. The suppression of a circulating lipoprotein lipase inhibitor, essential

for the microbiota-induced deposition of triglycerides in adipocytes was proposed as a possible mechanism.¹⁷ Furthermore, interesting differences in the microbiota composition were reported when genetically obese mice to normal-weight mice were compared.¹⁸ The obese mice had a greater presence of bacteria with a higher expression of enzymes related to energy extraction, bowel fermentation and to the reduction in stool residual calories. In a subsequent work, the microbiota from obese mice was transplanted to normal-weight mice and it was found that the latter developed obesity within two weeks,¹⁸ in agreement with the original hypothesis. These findings evidenced that the gut microbiota is a dynamic ecosystem of living microorganisms susceptible to environmental and pathophysiological alterations.¹⁸ Dietary habits, lifestyle, age, host genotype and exposure to antibiotics may affect the composition of the gut microflora.¹⁹ Translating and extending the findings from these animal studies to humans is currently an important area of research because of links to the systemic health of the host.

Indeed, the gut microbiota is nowadays considered a metabolic organ, which performs a wide range of functions including an important role in the physiology of energy homeostasis.²⁰ Commensal bacteria contribute to the digestion of nutrients otherwise inaccessible to humans, such as resistant starch, some oligosaccharides, unabsorbed sugars, alcohols and protein/amino acids. Carbohydrate fermentation leads to the generation of short-chain fatty acids (SCFA) including butyrate, acetate and propionate. These are an important energy source for the host, providing up to 10%-15% of a human's daily energy supply. They also influence cell differentiation and proliferation, ion absorption or vitamin production and contribute to the supply of amino acids required by human beings.¹¹ In the presence of fermentable carbohydrate substrates, colonic bacteria grow and synthesize protein and somewhere between 1% and 20% of circulating plasma lysine and threonine in adults is derived from the intestinal microbiota.²¹ Proteolytic fermentation generates polyphenols that induce anti-inflammatory, anti-oxidative and anti-ageing effects and also a proportion of the pool of SCFA, derived from amino acid fermentation. On the other hand, anaerobic metabolism of peptides and

proteins, known as putrefaction, produces some potentially toxic substances including ammonia, amines, phenols, thiols, and indols.¹¹ Additionally, commensal bacteria induce lipolysis leading to increased fat storage, hepatic de-novo synthesis of triglycerides and the alteration of bile acid metabolites with consequences to lipid metabolism in the host.³

The gut microbiota has also been shown to have a role in the obesity-linked low grade chronic inflammatory state of the host.²² Specifically the overgrowth of *Proteobacterium* produces reduction of the gut barrier protective bacteria.²³ These microorganisms act by altering the signaling pathways that link obesity with inflammation. Thus, bacterial lipopolysaccharide (LPS) has been proposed as a mediator for this outcome,^{6,24} since LPS is part of the outer membrane of gram-negative bacteria and is an endotoxin for the host.²⁵ Infiltration of LPS from the gut lumen into the bloodstream induces cytokines and triggers an inflammatory response.¹⁴ Such increased LPS levels have been described as “metabolic endotoxemia”²⁴ and many obesity-related comorbidities have been reported to correlate with circulating LPS concentrations.²⁵ Indeed, the microbiota can influence intestinal permeability and the physiological functioning of the intestinal barrier, which is essential to avoid LPS infiltration.

DIETARY STRATEGIES

Dietary strategies have been the mainstay of treatments to counteract overweight and obesity.²⁶ Diet is considered to be a major environmental factor influencing gut microbiota diversity and functionality.²⁰ Therefore, the effect of dietary patterns on gut microbiota conjointly and on weight-loss outcomes may become potential therapeutic strategies in managing metabolic health. Altered dietary intake not only affects energy balance but also has a major impact upon gut microbial composition and this can promote obesity and increase the risk of developing metabolic diseases,⁶ or vice versa, appropriate changes in the gut microbiota may promote weight loss and beneficial metabolic change. A weight loss intervention program, based on a calorie-restricted diet and increased physical activity in an obese adolescent population, was demonstrated to induce changes in the gut microbiota content and some of these changes correlated with weight loss and BMI z-score reductions.²⁰ This outcome is in agreement with other studies, showing that levels of *Bifidobacterium* were reduced in infants who became overweight at 7 years old compared with the higher level of *Bifidobacterium* in normal weight children.²⁷

In previous studies with adults, it has been also shown that obese people had fewer *Bacteroidetes* and more *Firmicutes* than lean controls before diet therapy.^{28,29} Subsequently, decreases in *Firmicutes* and increases in *Bacteroidetes* were correlated with body weight loss.^{6,30} It was also reported that changes in the faecal bacteria population began one week after caloric restriction,⁶ while another similar study found detectable changes within 24 hours of initiating a dietary intervention.³¹ These findings confirmed the hypothesis derived from animals that the gut microbiota is dynamic, although these studies disagreed with some earlier investigations, which had suggested stability over time and resistance to

perturbations.³²

In recent times, dietary strategies to counteract obesity and overweight states have been focused not only on the amount of calories prescribed, but also on the macronutrient composition (eg increased protein intake), the type of food (eg glycemic index or load) or the presence of specific bioactive compounds (omega-3 fatty acids, fibre or polyphenols). Therefore, future studies to evaluate the dietary influence on microbiota composition should also take such new aspects into account.

CARBOHYDRATE DIETS

Carbohydrates have been one of the most studied dietary components in relation to microbiota modifications. Gut microbes are known to be involved in the absorption of monosaccharides and it is generally accepted that carbohydrate fermentation results in beneficial effects for the host because of the generation of SCFA (Table 1).³³ Moreover, shifts in the composition of the gut microbiota in response to the total quantity of carbohydrate intake in obese people have been reported.³⁴ Thus, *Bifidobacteria* showed a significant reduction with decreased carbohydrate intake as well as some *Clostridium* subgroups (*Roseburia* and *Eubacterium rectale*), which correlated strongly with the reduction in stool butyrate levels (Table 1). The same outcome was found also in an obese group when analyzing high-protein/carbohydrate-reduced diets.³⁵ This kind of diet reduced *Roseburia/E. rectale* concomitant with a decrease in the proportion of butyrate in faecal SCFA and a major reduction of fibre-derived antioxidant phenolic acids (Table 1). These results were in agreement with those from a previous study where a low-carbohydrate to a fat-restricted diet were compared revealing a decreased *Bacteroidetes* number, which correlated with the carbohydrate-restricted diet.³⁶ The outcomes suggested that different dietary compositions have different influences on bacterial shifts and evidenced that it is necessary to take the dietary components into consideration in future studies.

Increased fibre intake has shown to have several beneficial effects on metabolic markers, although the mechanisms responsible are not completely understood. Thus, decreasing sugar and cholesterol absorption, the production of phytochemicals and other bioactive compounds, as well as anti-inflammatory properties have been proposed as processes involved in the healthy properties of fibre.³ Bacterial fermentation of undigestible components of whole-grain products is another key issue in trying to explain the effects found, as whole grains affect both the microbiota and obesity itself, and the interplay between them. Microbial fermentation of plant fibre produces phenolic compounds with antioxidant and antitumoral activities (Table 1).³⁵ High fibre content diets have been positively associated with *Bacteroidetes* and *Actinobacteria* presence,³¹ and with a reduced *Firmicutes*-to-*Bacteroidetes* ratio,³⁷ while dietary resistant starch might reduce the formation of harmful nitrogenous compounds. Thus, arabinoxylan-oligosaccharides enriched bread was observed to increased total bacterial populations and faecal butyrate concentrations in healthy volunteers.³⁸ Additionally, the treated group showed a trend to reduced protein-fermentation derived harmful acids. Furthermore,

Table 1. Shifts in gut microbiota derived from different dietary strategies of dietary modifications.

Dietary strategy	Basis/Mechanism	Affected species	Observed effects	References
Carbohydrate ↓	Related with beneficial effects because of the association with SCFA production and phenolic compounds, known to have anti-inflammatory effects.	<i>Bifidobacteria</i> ↓ <i>Clostridium</i> ↓ <i>Bacteroidetes</i> ↓	Decrease SCFA: Butyrate production. Decrease fiber-derived phenolic acids.	33, 34, 35, 36
Protein ↑	Proteolytic fermentation produces beneficial compounds, but putrefaction is considered detrimental for the host's health.	<i>Bacteroidetes</i> ↑ <i>Lactobacillus</i> ↑ <i>Bifidobacterium</i> ↑	Amelioration of obesity, inflammation and metabolic complications.	11, 31, 35
Mediterranean ↑	Widely accepted as a healthy dietary pattern, with many specific components (polyphenols, PUFA).	Polyphenols: <i>Prevotella</i> ↑ <i>Enterococcus</i> ↑ <i>Bifidobacteria</i> ↑ <i>Lactobacillus</i> ↑ <i>Bacteroides</i> ↑ <i>Clostridium</i> ↓ PUFA: <i>Lactobacillus</i> ↑	Improvement of obesity, lipid profile and inflammation. An adults' microbiome is not particularly enriched in genes involved in fatty acid metabolism.	6, 8, 52, 53, 54

SCFA: short chain fatty acids; PUFA: polyunsaturated fatty acids.

arabinogalactan has been associated with a statistically significant increase in the concentration of total bacteria, *Bacteroidetes*, *Faecalibacterium prausnitzii*, a delayed bifidogenic effect and a decrease of the pathogenic *Clostridium perfringens*.³⁹ On the other hand, fructo-oligosaccharides leads to a strong lactobacillogenic effect.³⁹ So, much interest in relation to prebiotics has been focused on non-digestible oligosaccharides, which have been described to change microbial composition.²¹ Actually, biological effects depend on gut microbiota composition and the subsequently derived metabolites.

Moreover, in a study comparing diet impact on gut microbiota in European children and those from rural Africa, it was observed that in Rural Africa, where the diet is rich in fibre, the children had a significant enrichment in *Bacteroidetes* and a depletion in *Firmicutes*, with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter* (which are known to contain a set of bacterial genes for cellulose and xylan hydrolysis), while these species were completely lacking in the European children.⁴⁰ They also found more SCFA in the African children, suggesting that the gut microbiota has co-evolved with the polysaccharide-rich diet of African individuals, allowing them to maximize energy intake from fibres, while also protecting them from inflammation and non-infectious colonic diseases.⁴⁰

Carbohydrates are considered to have beneficial effects on inflammation because of bacterial production of SCFA like butyrate, with the *Clostridium* cluster the most important in this aspect. Hence, SCFA are known to have anti-inflammatory effects that result from inhibition of transcription factor NF- κ B leading to a decreased secretion of proinflammatory cytokines (Table 1).⁶ An increase in the *Clostridium* group presence (*Faecalibacterium prausnitzii*, specifically), linked to higher resistant starch intake, has been associated with lower levels of circulating inflammatory parameters in patients after bariatric surgery. In contrast, lower proportions of this group of microorganisms were found in patients with type 2 diabetes and were related to a worsening of their low-grade inflammation and higher insulin resistance.⁶ Interestingly, in the same study, a negative association was also seen between *F. Prausnitzii* and HOMA-IR.

HIGH-PROTEIN DIETS

Increasing protein content of the diet has been one of the most intensely assessed variations in macronutrient distribution in order to manage body weight.³⁶ Available results are controversial but the prevalent idea is that moderately high protein diets help weight loss and/or weight maintenance.⁴¹ In relation to the gut microbiota, proteolytic fermentation produces beneficial compounds, but putrefaction is considered detrimental for the host's health (Table 1).⁴² This situation occurs in the distal bowel generating potentially toxic substances such as ammonia, amines, phenols and sulfides.¹¹

Epidemiological studies have associated meat-rich diets with colorectal cancer³⁵ and fermentation-derived toxic agents with dietary protein intake.⁴³ However, despite these indications, the relationship between gut health and protein fermentation has not been thoroughly investigated and there are not many human studies focusing on the

effect of high protein intake and microbiota changes. Generally, the protein proportion of the diet is increased by a reduction in the carbohydrate content, so that the consequences of such a carbohydrate reduction are found in high-protein diets as well as with protein fermentation toxic products. Additionally, a diet enriched in protein favours the *Bacteroidetes* group (Table 1).³¹ Fermentation of amino acids derived from dietary or host-derived proteins yields a much wider range of products. Faecal branched-chain fatty acids are indicative of fermentation of branched-chain amino acids and their faecal concentrations increase on high-protein diets,¹⁰ which can influence beneficial microbiota. In this context, dietary controlled studies in obese men following high protein/low carbohydrate intake during 3-4 weeks detected microbial changes, particularly reduction in *Collinsella aerofaciens*, *E. rectale*, *Roseburia*, and *Bifidobacterium* spp.^{34,35} A recent study assessing zonulin, a protein that increases intestinal permeability and participates in the development of intestinal innate immunity, showed that plasma zonulin was inversely proportional to protein percentage dietary intake.⁴⁴ Zonulin is considered as a potential marker of intestinal permeability, therefore, suggesting that protein intake may be associated with a reduction in intestinal permeability.

In addition to meat, dairy products are another important source of protein in our diet. There may be a role for these foods with microbiota modifications as they are a good matrix for probiotics, which when administered in adequate amounts, may confer a healthy benefit to the host, through different mechanisms.⁴⁵ In particular, *Lactobacillus* and *Bifidobacterium* have been shown to ameliorate obesity, inflammation, and associated metabolic complications (Table 1).¹¹ The mechanisms affecting health issues include inhibition of intestinal bacterial enzymes, stimulation of host immunity, competition for limited nutrients, inhibition of bacteria mucosal adherence and epithelial invasion, protection of intestinal permeability and control of bacterial translocation from the gut to the bloodstream.¹¹ There are few well controlled studies in humans, but it has been shown that 200 g per day of a fermented milk containing the probiotic organism *Lactobacillus gasseri* over 12 weeks produced significantly greater reductions in abdominal, visceral and subcutaneous fat, body weight and waist circumference compared with consuming fermented milk alone.⁴⁶

MEDITERRANEAN DIETS

The Mediterranean diet is widely accepted as a healthy dietary pattern, with demonstrated benefits for obesity treatment and improvement in associated cardiovascular risk markers.⁴⁷ A beneficial fatty acid profile,⁴⁸ with particular focus on monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) a higher antioxidants intake,⁴⁹ and the presence of other components such as fibre, vegetable protein and low glycemic foods are the main characteristics of this diet.⁵⁰ In relation to the specific foods consumed in the traditional Mediterranean diet, there is a high intake of olive oil, fruits, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meat and sweets; and a moderate consumption of red wine with

meals.⁴⁷ Polyphenols antioxidants are specifically consumed in the diet through different products such as tea, coffee, wine, fruit, vegetables and chocolate.⁵¹ A recent study in healthy humans comparing red wine intake with de-alcoholized red wine and gin intake observed changes in the distribution ratio of different genera within the *Bacteroidetes* and *Firmicutes*.⁸ The investigations reported that drinking red wine induced an increase in the number of *Enterococcus*, *Bacteroides* and *Prevotella* as well as an important decrease in the *Clostridium* genera, including *Clostridium perfringens*, an important pathogen associated with obesity, among others diseases (Table 1).⁵² This was explained by the increase in *Proteobacteria* known to degrade uric acid. The polyphenol-induced increase in *Bifidobacteria* was associated with a reduction of plasma cholesterol concentrations. A study with red wine-polyphenols also found that *Bifidobacterium* growth predicted a decrease in C-reactive protein, a marker of inflammation and a predictor of cardiovascular event risk in healthy subjects.⁸ So, red wine polyphenol intake may be related to an improvement in the obesity-related inflammatory state.

Another excellent source of antioxidants is fruit. In this context, the study of the bacterial metabolism of pomegranate demonstrated that a pomegranate product significantly enhanced the growth of *Bifidobacteria* and *Lactobacilli*, associated with various health benefits at the cellular and systemic levels (Table 1).⁵² This modulation of the gut microbiota could mediate the reduction of the high-fat diet induced hypercholesterolaemia. When considering total fat intake, a reduction in the *Bacteroidetes/Firmicutes* ratio after high fat diets has been reported,⁶ while fat restricted diets (together with higher carbohydrate intake) increased both *Bacteroides* and *Bifidobacterium* (Table 1).⁵³ Also, it has been found that high fat diets, independently of being high-saturated or high-monounsaturated, decreased total faecal microbiota.⁵³ However, it was not clear whether the crucial factor affecting microbiota is the elevated/reduced fat or the reduced/elevated carbohydrate content. Interestingly, increased endotoxemia was found to be associated with increased fat consumption in obese humans⁶ leading to an increased inflammation state.⁵⁴ Some studies have shown that a higher fat content of a diet involves a higher intestinal permeability and consequently, an increase in plasma LPS levels.⁵⁵ This phenomenon has been explained by the fact that the insoluble fraction contained in the LPS structure can be incorporated into micelles and absorbed into the chylomicrons in the postprandial period after a fatty meal.⁵⁶ Specifically, saturated fats have been positively associated with the *Bacteroides* group.³¹ An adult's microbiome is not particularly enriched in genes involved in fatty acid metabolism, but some interactions between PUFA and the microbiota have been described, suggesting that these fatty acids can positively influence the adhesion of *Lactobacillus* to the jejuna mucosa and these bacteria may have a potential regulatory effect on PUFA absorption (Table 1).⁵⁷ Nevertheless there is a lack of human studies regarding the role of specific fat types on the gut microbiota.

Conclusions

It remains widely accepted that diet has a large influence on the gut microbiota composition, although mechanistic studies are needed in order to determine those bioactive constituent(s) or metabolite(s) coming from the gut bacteria that are responsible for the described effects. Among the different dietary components, carbohydrates, specifically the non-digestible starches, seem to play a key role, particularly related to the formation of SCFA. The polyphenols occurring in the typical Mediterranean diet have shown certain beneficial properties. More studies are needed to determine a possible effect of protein intake on microbiota composition changes. What is even more obvious is that more studies in humans are needed examining every component of the diet to assess the effects on the microbiota and to evaluate these effects in the context of a whole diet.

More research is needed regarding diet-microbiota-inflammation associations, as there are not many studies that explore this connection. Probiotic therapy offers an intriguing approach to promote host health via delivering anti-inflammatory mediators.

Although more work is needed, specific dietary factors (carbohydrate, protein and Mediterranean food) have been shown to have an influence on the gut microbiome composition, meaning that there is an opportunity to prevent and treat obesity.

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AUTHOR DISCLOSURES

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Review Article

The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state

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地中海、碳水化合物和高蛋白饮食在治疗肥胖时对肠道微生物组成的影响和相关炎症状态

肠道微生物的作用在理解肥胖发生和发展的过程越来越重要。膳食策略被用作减肥的一个主要工具，现今，其专注点不仅仅是限制卡路里，而是涉及到膳食的各个方面。此外，饮食是影响肠道微生物组成的一个重要因素。因此，除限制能量摄入之外，治疗肥胖的饮食策略还要考虑到宏观营养和微观营养对肠道微生物组成的影响。本综述的目的旨在收集整理不同的饮食组成对人类肥胖和炎症相关的肠道微生物影响的现有数据。虽然还需要更多的工作，已有证据显示特定的饮食因素（碳水化合物，蛋白质和地中海食物）对肠道微生物的组成确有影响，意味着有可能通过改变肠道微生物来预防和治疗肥胖。

关键词：肥胖、营养、肠道微生物、饮食计划、炎症