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Gut microbiome and Mediterranean diet in the context of obesity. Current knowledge, perspectives and potential therapeutic targets

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ABSTRACT

Mediterranean Diet has been recognized as one of the healthiest and sustainable dietary patterns worldwide, based on the food habits of people living in the Mediterranean region. It is focused on a plant-based cuisine combining local agricultural products and moderate intake of fish. As eating habits seem to exert a major impact on the composition of gut microbiota, numerous studies show that an adherence to the Mediterranean diet positively influences the microbiome ecosystem network. This has a profound effect on multiple host metabolic pathways and plays a major role in immune and metabolic homeostasis. Among metabolic disorders, obesity represents a major health issue where Mediterranean Dietary regime could possibly slowdown its spread. The aim of this review is to emphasize the interaction between diet and gut microbiota and the potential beneficial effects of Mediterranean diet on metabolic disorders like obesity, which is responsible for the development of many noncommunicable diseases.

1. Introduction

The Mediterranean Diet (MedDiet) can be described as a dietary pattern mainly found in Greece, Italy and other countries surrounding the Mediterranean Sea, where people cultivate, among other crops, olives and produce oil. It seems that, since the early 1960s, Mediterranean inhabitants share common eating habits following a diet with many similarities. The MedDiet was initially published by Ancel Keys in 1978, who initiated a multi-country epidemiological study "the Seven Countries Study" in 1956. Yet, MedDiet gained recognition and attention after the International Conference of Harvard School of Public Health in 1993, organized by Oldways Preservation and Exchange Trust and the WHO/FAO Collaborating Center for Nutritional Epidemiology [1,2]. This diet is based primarily on vegetables, legumes, fresh fruits and whole grains and the principal source of fat comes from olive oil. It also includes moderate consumption of fish, dairy products (e.g. cheese) and poultry, very low intakes of red meat, refined carbohydrates and sweets and a moderate consumption of red wine accompanying meals [3].

The first time that the word microbiome emerged in literature was in 2001 by Joshua Lederberg when he included all the commensalism and pathogenic microorganisms of human body [4]. Humans have a complex ecosystem with close interactions. They are colonized by 10−100 trillions of symbiotic microbes that carry approximately 150 times more genes than the entire human genome [6]. During the last decades, improvements in culture-independent methodologies namely Next Generation Sequencing (NGS), expansion of bioinformatics and huge projects as Human Microbiome Project in 2007, contributed and shed light in human microbiome's functions [5]. Dietary habits influence the microbial

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populations, especially in the gut where microbes thrive and demonstrate complex interactions affecting variously human health. There is enough evidence providing the close relationship between diet and gut microbiome [6–8].

Human microbiota has a vital role to play in human health and disease. Irrespective of the technological advances in the past few years, the world has failed to restrain the raise of obesity as a pandemic disease that affects people across the world. The microbiome and especially gut microbiome represents numerous interactions with dietary habits and potential causality of different metabolic disorders such as obesity. As Patrice Cani very accurately questioned in 2017: Gut microbiota-at the intersection of everything? [9].

In this review, we aim to provide an overview of MedDiet and present how adherence to a diet, especially MedDiet, can affect gut microbiota in experimental and clinical studies with potential benefits in the context of obesity. We also refer to several studies which describe the microbial ecology in obesity and mention the microbiota effect on metabolic disorders and especially to obesity.

2. A short digest of Mediterranean Diet

Countries around the Mediterranean basin are not only known for their natural beauty and their pleasant climate with warm summers and mild winters, but also for their cuisine rich in colors and flavors, which reflects the strong connection of the inhabitants with nature. The MedDiet represents a dominant eating model of these countries in the broad geographical area surrounding the Mediterranean Sea. It was first identified in the early 1960s and later demonstrated by the Mediterranean Diet Pyramid, which was created by the Oldways Preservation Trust, the World Health Organization and the Harvard School of Public Health in 1993 [10].

MedDiet is rich in plant foods providing a variety of healthy nutrients. It includes high consumption of fresh vegetables, legumes, olives, fruits, seeds and cereal (mainly whole grains), with olive oil being the principal source of fat and moderate intakes of poultry, eggs, dairy products (mostly in the form of cheese or yoghurt) and red wine accompanying meals. Additionally, large portions of fish and seafood replace red meat which is consumed occasionally and in small quantities [10,11].

MedDiet based on a wide range of plant foods and nutrient-rich foods promotes, in general, a healthy lifestyle. It is a lifestyle encompassing, together with nutrition, physical exercise and companionship, sharing food with family and friends. One of its outstanding characteristics is the importance of family meals with all the members from different generations, sitting together, eating healthy and drinking red wine. It promotes well-being and it is related to longevity with low prevalence of chronic diseases [11,12]. Analyses of the diet depict lots of healthy and protective substances, providing high amounts of fiber, a balanced ratio of omega-6/omega-3 (ω6:ω3) essential fatty acids, natural antioxidants and vitamins [13]. As a result, many clinical and epidemiological studies have reported that MedDiet is associated with a lower risk of cardiovascular diseases [14], type II Diabetes [15,16], incidence of Parkinson's disease and Alzheimer's disease [17], low-grade inflammation [18], metabolic syndrome [19], obesity [20] and Chron's disease [21]. Oddly enough, there is a gap of knowledge considering the exact mechanisms for these beneficial effects and only recently the gut microbiome's crucial role emerged as for a common platform for interactions [22].

It may be beneficial in slowing down osteoporosis [23], promoting anticancer mechanisms [24] and reducing the risk of depression [25]. In addition, studies reported beneficial effects of adherence to MedDiet during pregnancy associated with a lower risk of preterm birth and fetal growth restrictions [26,27]. It is of paramount importance to follow a diet containing different foods and nutrients and not just one or two ingredients in order to prevent non-communicable diseases, such as cardiovascular events, and adopt the entire eating pattern for better results. Altogether, MedDiet can be related to a better quality of life, reducing mortality rate due to chronic diseases and prolonging lifespan.

3. Gut microbiota and its close relationship to diet

Trillions of microorganisms live on and within humans and play a major role in human health and disease. In 2007 the Human Microbiome Project started a research project using sequencing methods in order to identify and describe the microbial flora [28,29]. The number of microbes colonizing the intestine, termed 'gut microbiota' is estimated to be 10 times greater than that of the cells of human body and to carry 150 times more genes than that of the entire human genome. In human intestinal pathogenesis, commensal and symbiotic microbial communities thrive. It is also estimated that there are around 1000 species in the gut, with the most represented Phyla to be Firmicutes (e.g. Clostridium, Lactobacillus) and Bacteroidetes (e.g. Bacteroides, Prevotella) representing ~60% of gut microbiota, followed by Proteobacteria (e.g. Escherichia, Helicobacter) and Actinobacteria (e.g. Bifidobacterium) [30,31].

Gut microbiota begins to develop from birth and colonization by Bifidobacterium occurs within four days after birth [32]. Mode of delivery, vaginally or by caesarian section, and feeding type are major factors influencing the neonatal gut microbiota composition [33]. For instance, breast-fed infants' gut flora is characterized by an increased concentration of Bifidobacterium species, while infants under artificial feeding carry lower concentration of, or do not carry, Bifidobacterium and show a reduction of microbial diversity [32,34,35].

The gastrointestinal microbiota composition changes during a human's life, and major differences have been reported among people and between different geographical regions. Multiple factors affect the selection of microbial community composition, including both genetic and environmental factors, particularly geographic location, lifestyle, hygienic conditions, urban or rural living and the use of antibiotics. Specifically, antibiotics, either administered for therapy or by low-dose exposure through the food-chain seem to affect the bacterial microbiota causing dysbiosis [36]. Animal models have shown that administration of subtherapeutic doses disturb the gut microbiome and lead to increase of adipose tissue [37].

Evidence from animal and human studies depict that the host exercises control over the population of gut microbiota, through many host molecules such as microRNA, hormones, cytokines and metabolites, which interact with the microbiome and induce alterations in the growth or behavior of bacteria [38]. Many of these molecules have been shown to interact directly with the microorganisms. Extracellular vesicles are proposed to help to carry these molecules to bacteria for increased uptake [38].

According to the majority of studies, dietary habits seem to have a major impact on gut microbiota and play a significant role in shaping its composition [31,39,40]. The high-fat diets modify the gut microbiota negatively leading to dysbiosis, while plant-based diets affect it positively. As a result, the intestinal microbiome may provide evidence of eating habits and reflects whether one follows a healthy or not healthy diet [41].

It is actually more than an axiom that the gut microbiota is involved in multiple host metabolic pathways and plays a vital role in maintaining immune and metabolic homeostasis. It has the potential to contribute to the digestion of nutrients which otherwise could not be absorbed by the human body and to take part in the

metabolism of carbohydrates leading to the generation of short chain fatty acids (SCFA), such as butyrate, acetate, propionate, which are important energy sources for the host. Moreover, it takes part in biosynthesis of vitamins, lipolysis and it is essential in the creation of intestinal mucosa. It protects its host against pathogenic microorganisms by producing antimicrobial compounds and preventing their colonization. However when the microbiome homeostasis is disturbed, dysbiosis leads to disease [6,42,43].

After the Industrial Revolution, new technological advances appeared in the food industry leading to lifestyle changes and to a modern dietary path, the Western pattern diet. The above-mentioned diet is characterized by high consumption of red meat, processed meat, fried foods cooked with refined vegetable oils, high-fat dairy products, refined grains and high-sugar drinks, not present in the pre-agricultural diet. As a consequence, high intake of saturated fats and low intake of fiber lead to a rising health risk, alterations in gut microbiota and to an increased risk of metabolic disorders [44–46].

MedDiet, on the other hand, is widely accepted as a healthy pattern of diet which impacts beneficially the gut microbiota. PREDIMED test [47] described microbiota composition and diversity in adherence to MedDiet by 16S rRNA gene sequencing and specific quantitative polymerase chain reaction. The metabolic activity of microbiota was determined by quantification of SCFAs on high performance liquid chromatography (HPLC). The results revealed that the bacterial profile of those following MedDiet consists of a greater presence of Bacteroidetes and a lower ratio Firmicutes/Bacteroidetes, alike those who consume less animal protein [47,48]. The PREDIMED trial depicted that a plant-based diet was positively associated to a remarkable diminution in all-cause mortality. Overall, the Bacteroidetes phylum is more abundant in plant-based diets compared to omnivores [40] and this higher proportion of Bacteroidetes is probably related to increased consumption of fiber [49]. Mitsou et al. concluded that those adhered to MedDiet showed lower levels of *Escherichia coli* (E.coli) and higher ratio of Bifidobacteria/E. coli [50]. Pisanu et al. [51], showed that after following a specific MedDiet, an increase in Proteobacteria was observed, an increase in Bacteroides uniformis and Prevotella stercorea was also observed and families belonging to Firmicutes phylum were depleted, for instance Ruminococcus. Several Firmicutes belonging to the Lachnospiraceae family changed as well, with a decrease in Roseburia, Roseburia faecis, and Pseudobutyrivibrio xylanivorans [51] (see Table 1). High consumption of animal protein, saturated fats and sugars affect negatively gut microbiota diversity [47]. A high Firmicutes/Bacteroidetes ratio is related to many disorders, such as type 2 diabetes [52] and obesity [53] and is commonly associated with the western diet.

Amongst characteristics of MedDiet is the high intake of fibre and particularly of insoluble fibre in contrast to the Western diet. High intake of fruit, vegetables and legumes is associated with an increase in fecal SCFA levels and a high proportion of fibre-degrading microorganisms. Aadherence to MedDiet and high intakes of fibre increase Bacteroidetes and decrease Firmicutes. Studies indicate that the gut microbiota production of SCFA can reduce several inflammatory and allergic diseases [54]. Prevotella also seems to be common in plant-rich diets and it has been linked to MedDiet and vegetarian diets. On the other hand, diets rich in animal protein and fat (Western diet) are related to higher urinary trimethylamine oxide (TMAO) levels and L-Ruminococcus appeared to be linked to those diets, in contrast to plant based diets (such as MedDiet), where urinary TMAO levels are significantly lower. TMAO is associated with risk of atherosclerosis and cardiovascular diseases [40,55]. In addition, dietary phenolic substances from vegetables, fruits, cereals, coffee, dark chocolate or wine, may modify the microflora composition, exhibit prebiotic effects and have antimicrobial action against pathogenic microflora [56]. Generally, long term plant-based diets have been associated with richer and various phylogenetic fecal microbiota, in contrast with Western diet in which specific bacterial lineages are eliminated, influencing negatively the immune system and increasing the risk of multiple diseases [54,57].

Recently two exceptional studies were published in the journal Gut. The first, by Meslier et al. [58], pointed out that it is the quality and not the quantity of calories that matters and, also, revealed that MedDiet remodels the gut microbiome composition and causes lipid profile alterations leading to reduced risk factors (see Table 1). The other research, conducted by Ghosh et al. [59], strongly suggested that MedDiet improves frailty and cognitive function in the elderly by modifying gut microbiota. Taken together, the MedDiet is linked with lower inflammation and healthy aging. There are also clinical trials [60,61](see Table 1), studying the MedDiet-induced changes of the gut microbiome in obese subjects.

4. Obesity and the perspective of gut microbiota

World Health Organization estimated that worldwide, in 2016, more than 1.9 billion adults were overweight and over 650 million of these were obese. The worldwide prevalence of obesity nearly tripled from year 1975–2016. Additionally, the prevalence of overweight and obesity among children and adolescents has risen from 4% in 1975 to over 18% in 2016, with more than 124 million children and adolescents being obese in 2016 [62]. Obesity is characterized by excess of adipose mass. The adipose tissue acts like an endocrine organ, secreting a wide variety of inflammatory adipocytokines, such as leptin, adiponectin, tumor necrosis factor alpha (TNF-alpha), which lead to systemic inflammation, insulin resistance and metabolic disorders-linked to obesity. In summary, excess weight and obesity are linked to many diseases and high rate of mortality causing a problem of gargantuan proportions.

Body Mass Index (BMI) is commonly used to classify obesity. BMI is defined as the body mass divided by the height in meters squared [kg/m^2]. A raised BMI leads to pathological conditions such as ischemic heart diseases, diabetes, musculoskeletal disorders (e.g. osteoarthritis), and several forms of cancer, whilst obesity is also linked with a higher risk of autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis and psoriatic arthritis [62–66]. Moreover, childhood obesity increases the likelihood of obesity in adulthood. Chronic diseases such as type 2 diabetes, hypertension and hyperlipidemia that have previously only been seen in adults, are now seen in obese children and adolescents as well [67]. The causes of obesity appear to be multiple. Genetic background, a sedentary lifestyle and diet are some of them [68].

Gut microbiome plays a major role in the metabolism of the host and its disturbed composition could be an important parameter for weight accumulation [69]. Dysbiosis contributes to the onset of several disorders [69]. Gut microbiota has been shown to differ in obese individuals and most studies show low diversity and variety in the microbial composition in obese people compared to lean subjects [70,71]. In obesity, elevated branched-chain amino acids (BCAAs) and aromatic amino acids have been found, such as in insulin resistance and Type 2 diabetes. Obesity is also linked to increased bile acid synthesis with an impaired transport and may lead to increased levels of TMAO [70,71]. In summary, metabolic pathways and fat accumulation in obesity can be reflected in gut microbiota.

Studies [72–78] in obese mice and humans manifest significant alterations of phyla in the intestine with a great reduction in Bacteroidetes and a proportional increase in Firmicutes, with high levels of Lactobacillus species and, specifically, higher levels of

Table 1
Representative studies and clinical trials demonstrating the gut microbial ecology in relation to obesity including diet interventions.

Author	Method (n men)	Results
Meslier et al., 2020 [58]	n = 82 overweight and obese subjects 8-week randomised controlled trial. 43 participants consumed MedDiet and 39 maintained their regular diets Targeted quantification of bile acids in the feces by ultra-high-performance liquid. Chromatography mass spectrometry. DNA libraries were sequenced using the Ion Proton Sequencer (ThermoFisher Scientific, Waltham, USA), with a minimum of 20million 150bp high-quality reads generated per library.	In the MedDiet group: Gut microbiome changes with increased levels of fibre-degrading Faecalibacterium prausnitzii and of genes for microbial carbohydrate degradation linked to butyrate metabolism. Ruthenibacterium lactatiformans, Flavonifractor plautii, Parabacteroides merdae, Ruminococcus torques and Ruminococcus gnavus were significantly reduced
Pisanu et al., 2020 [51]	n = 23 obese subjects 3 months of nutritional intervention (MedDiet). Fecal samples analyzed by Illumina MiSeq sequencing of the 16S rRNA gene.	Increase in the abundance of several Bacteroidetes taxa (i.e., Sphingobacteriaceae, Bacteroides spp., Prevotella stercorea) and a depletion of many Firmicutes taxa (i.e., Lachnospiraceae members, Ruminococcaceae and Ruminococcus, Veillonellaceae, Catenibacterium, Megamonas). In addition, the phylum Proteobacteria showed an increased abundance, while the genus Sutterella, within the same phylum, decreased after the intervention.
AdriánCortés-Martín et al., 2020 [88]	n = 415 (Spanish children and adolescents) High-performance liquid chromatography with diode array detection coupled to electrospray ionization and ion-trap tandem mass spectrometry (HPLC-DAD-ESI-IT-MS/MS) (sample of urine) and ultra-high performance liquid chromatography coupled with electrospray ionization-quadrupole-time-of-fight-mass spectrometry (UPLC-ESI-QTOF-MS).	Stratification of the children according to their urolithin metabotypes UM-A,UM-B, UM-0, which could be early biomarkers, in the case of UM-B and UM-0, of a dysbiotic-prone obesity-associated microbiota. The Coriobacteriaceae family, and probably the Proteobacteria phylum, more abundant in obese children and in UM-B. The microbiota associated with UM-0 has been reported to show low diversity, which could be indicative of an obesity-prone microbiota.
ClinicalTrials.gov Identifier: NCT04453150 (Clinical trial/Recruiting), First posted: 2020 [60]	n = 150. Obese subjects. Dietary intervention with 4 types of diet (among them MedDiet).	Changes in gut microbiota composition. Change from baseline in 16S rRNA amplicons of fecal community DNA at 3 months and 6 months
ClinicalTrials.gov Identifier: NCT03071718 (Clinical trial' Completed), Last Update posted: 2019 [61]	n = 82. Obese/overweight subjects following Mediterranean diet for two months and control subjects.	Changes in fasting plasma lipids (Total-, LDL-, and HDL-Cholesterol, Triglycerides), in faecal levels of short chain fatty acids, in faecal microbiome, in fasting inflammatory blood markers (plasma C-reactive protein)
Sarmiento et al., 2019 [86]	FISH 72 individuals Lean n = 24, overweight n = 24, obese n = 24	Fusobacterium, Enterococcus, E.coli were higher in individuals with obesity, compared with lean individuals.
Garcia-Mantrana et al., 2018 [48]	27 volunteers (16 females and 11 males) qPCR	Verrucomicrobia phylum significantly more abundant in the normal weight group. Members of the family Christensenellaceae and the genera Desulfovibrio and Oscillospira were more abundant in lean individuals. Streptococcaceae was associated with those individuals with higher BMI.
Ottosson et al., 2018 [85]	Sequencing 674 individuals (lean, overweight, obese)	Positive correlation between BMI and Lachnospiraceae (Blautia, Dorea and Ruminococcus), and negative correlation between BMI and SHA-98
Jinatham et al., 2018 [84]	qPCR 42 individuals Lean n = 21, overweight n = 10, obese n = 11	Bacteroidetes, Firmicutes, Staphylococcus, Akkermansia muciniphila, Methanobacteria: lower in individuals with obesity, compared with lean. Ruminoccocus, Christensenella minuta, γ-Proteobacteria, Akkermansia Municiphila: lower in individuals with obesity, compared with overweight.
Ignacio et al., 2016 [83]	84 children: obese (n = 30), overweight (n = 24), lean (n = 30). Culture techniques and quantitative determination by quantitative PCR	Bacteroides fragilis group, Lactobacillus spp. found at high concentrations in obese and overweight children. The concentration of Bifidobacterium spp. was high in the lean group; negative correlation between Bifidobacterium spp. and BMI
Hu et al., 2015 [81]	Fecal samples from 134 Korean adolescents (67 obese, 67 normal), DNA extraction, Pyrosequencing of 16S rRNA	No significant differences at phylum level, between Bacteroidetes, Firmicutes, Proteobacteria in normal and obese adolescents. Proportion of Bacteroides was higher in normal children Proportion of Prevotella was higher in obese. Both Bacteroides and Prevotella belong to the same Phylum, so no apparent difference at Phylum level.
Kasai et al., 2015 [77]	Fecal samples from non-obese (n = 23) and obese (n = 33) subjects. Terminal restriction fragment length polymorphism analysis, next-generation sequencing, Metagenome@KIN software	A higher Firmicutes to Bacteroidetes ratio in obese subjects.
Million et al., 2012 [82]	qPCR for different strains and culture on a Lactobacillus-selective medium, 115 individuals, Obese n = 68 and lean-controls n = 47 (feces)	Higher Lactobacillus reuteri (Phylum: Firmicutes) levels in obesity, Decrease of Bacteroidetes, Bifidobacteria, Lower concentration of Methanobrevibacter smithii in obese subjects
Geurts et al., 2011 [75]	Pyrosequencing and phylogenetic microarray analysis of 16S rRNA gene sequences in obese and diabetic leptin-resistant mice	Higher abundance of Firmicutes, Proteobacteria in obese
Schwiertz et al., 2010 [79]	qPCR using 16S rRNA gene-targeted group specific primers (feces), 98 participants Lean n = 30, overweight n = 35, obese n = 33	Proportion of Bacteroidetes increased in overweight and obese participants. Higher SCFA concentrations (fecal samples) in obese, highest increase for propionate
Murphy et al., 2010 [76]		

Table 1 (*continued*)

Author	Method (n men)	Results
	SCFA by gas chromatography, microbial composition by metagenomic pyrosequencing	Increase in Firmicutes, Reductions in Bacteroidetes in obese SCFA increased (but this did not persist with time)
Waldram et al., 2009 [73]	FISH and DGGE methods (feces)	Numbers of total bacteria lower in obese, lower Bifidobacteria, higher Clostridium, Halomonas and Sphingomonas sp. present in obese (denser band in obese)
Turnbaugh et al., 2009 [78]	16S rRNA gene sequencing from 154 individuals twins and mothers, obese or lean (feces)	Reduced bacterial diversity in obesity. Reduced levels of Bacteroidetes in obese participants
Duncan et al., 2008 [80]	FISH (feces), participants on weight-loss diets and weight maintenance	No difference in the proportion of Bacteroidetes between groups

Lactobacillus reuteri. However, other studies have shown conflicting results, in which fecal concentrations of Bacteroides were positively correlated with the BMI and Bacteroidetes were increased in obese people [79], whilst other researchers did not find remarkable alterations in the proportion of the two dominant Phyla [80,81]. Differences may be due to different methodologies applied as well as interpersonal variation [70]. Furthermore, the genus of Bifidobacterium (belonging to the phylum Actinobacteria) that is known for having anti-inflammatory effects, appears to be decreased in obese people compared to lean subjects [82]. A negative correlation between BMI and Bifidobacterium spp. was also observed by another research group, that studied childhood obesity and the correlation between BMI and faecal microbiota from children [83]. The same study revealed that Bacteroides fragilis group and Lactobacillus spp. were found in higher concentrations in obese and overweight children than in lean ones. Also, individuals with obesity showed lower counts for Bacteroidetes, Firmicutes, Staphylococcus, Akkermansia muciniphila, Methanobacteria, compared with lean individuals and lower counts for Ruminoccocus, Christensenella minuta, γ-Proteobacteria, Akkermansia municiphila, compared with overweight [84]. Verrucomicrobia phylum was significantly more abundant in the normal weight group. Members of the family Christensenellaceae and the genera Desulfovibrio and Oscillospira were more abundant in lean individuals and Streptococcaceae was associated with those individuals with higher BMI [48]. Positive correlations were found between BMI and Lachnospiraceae (Blautia, Dorea and Ruminococcus), and negative correlations were found between BMI and SHA-98 [85]. Fusobacterium, Enterococcus, E. coli were higher in individuals with obesity, compared with lean individuals [86](see Table 1). Other studies [74,87] demonstrated that there is a relationship between energy intakes and plasma lipopolysaccharides (LPS) concentration. Specifically, the population of Gram-negative bacteria, known to have LPS on their bacterial cell walls, seem to increase in gut microbiota in high-fat diet. Chronically, this leads to high plasma LPS levels causing metabolic endotoxemia and gut, hepatic and adipose tissue inflammation.

According to research by AdriánCortés-Martín et al. [88], microbiota-associated Urolithin Metabotypes (UM-A,UM-B or UM-0) can predict obesity in childhood. Gut microbiota associated with UM-B and UM-0 individuals show a dysbiotic-prone pattern. On the other hand, the microbiota associated with UM-0 has been reported to show low diversity, which could be indicative of an obesity-prone microbiota. Stratification of the children according to their urolithin metabotypes, could be early biomarkers, in the case of UM-B and UM-0, of a dysbiotic-prone obesity-associated microbiota.

Furthermore, experiments with animal models, especially with humanized germ-free or genetically modified mice, are helpful for understanding the associations among dietary pattern, metabolism and gut microbiota synthesis, but further clinical studies are required to confirm the effects of gut microbiota on human metabolic disorders [89].

5. Mediterranean Diet as a tool against obesity

Obesity is a serious global health problem that is predicted to increase in the coming years. Obesity and its associated inflammation are potentially reversible by losing weight and decreasing fat mass and proinflammatory adipokines. Diets rich in bioactive compounds, such as ω-3 fatty acids (ω-3 FAs) and polyphenols, seem to be significant contributors [90].

There is an increasing number of studies from the scientific community examining the relation between MedDiet and obesity, and most provide evidence that an adoption of MedDiet is associated with weight loss and less adiposity, also decreasing the risk of non-communicable diseases associated with modern life [3,91]. MedDiet is mainly characterized by the consumption of virgin olive oil, legumes, vegetables, fruits, cereals (mainly whole grains), fish and red wine, foods which permit high intakes of phenolic compounds (called polyphenols) and ω-3 FAs. There are many health benefits from MedDiet, as polyphenols play an important role with a variety of health promoting activities such as anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic and antiadipogenic effects, ameliorating the lipid profile and adiposity. The absorption of the ingested polyphenols in the small intestine is low (less than 10%) and the rest of polyphenols interfere with gut microbial community, influencing the microbiota composition positively for human health. However, the underlying mechanisms and the general effect of such bioactive agents needs further investigation [56,92–95].

Regarding ω-3FAs, it is obvious that consumption of typical Mediterranean foods leads to appreciable intakes of ω-3 FAs which are reported to improve metabolic disorders associated with obesity including chronic inflammation, diabetes and dyslipidemia. Numerous studies show that ω-3 FAs exert their beneficial effects through adipose tissue metabolism [96]. In fact, ω-3 FAs have been claimed to act against low-grade inflammation in adipose tissue and have been widely reported to have protective effects in obesity and other chronic inflammatory conditions [97]. Micallef et al. [98], observed significantly lower plasma concentrations of ω-3 FAs in obese people compared to normal-weight individuals. Oh et al. [99], in an animal model, shows that G protein-coupled receptor 120 (GPR120) functions as a ω-3 FA receptor/sensor in proinflammatory macrophages and mature adipocytes with broad anti-inflammatory effects. DHA (docosahexaenoic) and EPA (eicosapentaenoic), which are major ω-3 FAs in fish oil, mediate, by signaling through GPR120, potent anti-inflammatory and antidiabetic effects in obese mice. Several other studies have demonstrated that ω-3 FAs are able to modulate leptin gene expression and as leptin is a hormone involved in the regulation of food intake, body fat storage and insulin signaling, a diet enriched in ω-3 FAs results in a higher rate of weight loss [100–102].

Data from studies show that consumption of MedDiet improves the lipid profile by lowering total cholesterol levels in plasma and specifically, LDL-cholesterol [58] (Table 1). MedDiet is found to be more efficient for long-term weight loss among overweight or

obese individuals compared to other low-fat diet patterns [3]. Several mechanisms could explain why MedDiet is protective against weight gain and, firstly, the fact that it contains high consumptions of food with low energy - density, low in fat and calories, such as vegetables, fruits and legumes, which are also good sources of fiber, inducing satiety and leading to lower energy intake. By consuming more fruits and other low energy-density foods, the total energy density of the diet is decreased [103]. Additionally, the increased fibre content of a meal has been shown to increase plasma cholecystokinin levels, and other appetite − regulating hormones, enhancing satiety [104]. Moreover, high consumption of fibre generates more production of SCFAs by intestinal bacteria. Dietary fibers are contributing as energy sources for gut microbiota [105]. Therefore, obese people who adopted the MedDiet pattern achieved a restructuring of the gut microbiome dysbiosis such as increase in Bacteroides, Prevotella and other bacterial species known for their ability to metabolize carbohydrates into SCFA [106]. These fatty acids, mainly composed of acetate, propionate and butyrate, have many favorable effects, including the activation of hepatic AMP-activated protein kinase (AMPK), which functions as a regulator of metabolic homeostasis [105,107]. AMPK activity is stimulated by changes in cellular AMP/ATP ratio. Binding of AMP to AMPK allows it to be phosphorylated on Thr-172 and activates the kinase. Hence, the SCFA activation of AMPK could be explained by an increased AMP/ATP ratio. High fiber diet leads to higher production of SCFA in the colon and, as consequence, to higher concentration of SCFA in the portal vein, which can activate the AMPK in the liver [97]. SCFAs act as signaling molecules and regulate different biological pathways in the host [105]. Also, unsaturated fats stimulate greater energy expenditure, diet-induced thermogenesis and fat oxidation, preventing weight gain, in contrast to saturated fat [108].

Hence, MedDiet seems to be beneficial against obesity, in contrast to Western diet. Shively et al. showed that MedDiet reduced triglyceride levels and protects against hepatosteatosis, whereas Western diet increased caloric intake and body fat, insulin resistance and led to hepatosteatosis after 2.5 years [109]. Zinöcker and Lindseth emphasize that there is a strong association between Western diet and obesity, as Western diet causes changes in gut microbiome leading to obesity, metabolic disorders and inflammation [110].

6. Conclusion

The Mediterranean diet is a healthy dietary choice that incorporates the traditional eating and living habits of people living in countries around the Mediterranean region, including Greece and Italy. In general, it is characterized by consumption of a variety of foods and places a great emphasis on fresh fruits, vegetables, legumes, whole grains, fish and olive oil, foods rich in polyphenols, flavonoids, vitamins and antioxidants. The daily intake of dietary fiber is significantly increased as well as the dietary vegetable: animal protein ratio. There is also a significant reduction in saturated fat consumption and an increase in polyunsaturated fat intake.

Specific dietary patterns are associated with specific microbiome alterations and healthy diets can contribute to host-gut microbiome interactions in a positive manner, establishing effective pathways to prevent diseases. Considering the knowledge derived from studies using new technologies as metabolomics and metagenomics, changes in the habitual diet in favor of MedDiet pattern could modulate gut microbiome ecosystem which in turn could potentially scale up the benefits for health overall.

Thus, MedDiet seems to have beneficial impacts to the gut microbiome promoting a healthy life and could be a useful tool against obesity. As obesity is increasing worldwide at an alarming rate, it constitutes a serious global public health problem. Numerous health consequences are associated with obesity, including hyperlipidemia, high blood pressure, cardiovascular diseases, type 2 diabetes mellitus, chronic kidney disease, osteoarthritis and certain forms of cancer, which lead not only to chronic conditions that reduce the overall quality of life but also to an increased mortality rate.

Some approaches include weight loss medication and bariatric surgery, but they appeared to have negative effects, demand high expenses and do not show long-term results [111,112]. Contrarily, and as mentioned, adoption of a healthy diet pattern could be a significant and promising contributor. Furthermore, results from studies show that probiotics supplementation reduce adipose tissue mass [113,114] and prebiotics, defined as non-viable compounds in food which induce the growth and activity of beneficial microorganisms, could also prevent and treat obesity via gut microbiota modulation [71,115]. There are many natural sources of prebiotics like legumes, beans, starchy fruits and cereals [71].

Over the last years, our knowledge on gut microbiota composition has been expanded but there is a need of more studies to be presented for a better strain-level identification. In addition, numerous studies have demonstrated the influence of specific habitual diet patterns on gut microbiota composition and diversity. Nevertheless, more studies are required to investigate the relationship between gut microbiota and obesity in order to determine the mechanisms involved and show how diet can manipulate the microbiota providing health benefits.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

BCAAs	Branched-Chain Amino Acids
BMI	Body Mass Index
DGGE	denaturing gradient gel electrophoresis
FISH	Fluorescence in situ hybridization
GPR120	G Protein-coupled Receptor 120
LPS	Lipopolysaccharides
MedDiet	Mediterranean Diet
qPCR	quantitative polymerase chain reaction
SCFA	Short-Chain Fatty Acids
TMAO	Trimethylamine N-oxide
UM	Urolithin Metabotypes
ω-3 FAs	omega-3 Fatty Acids

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