Review

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Despoina Koumpouli , Varvara Koumpouli , Antonios E. Koutelidakis *

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Review

Functional Foods, Gut Microbiome and Association with Obesity and the Metabolic Syndrome: A Literature Review

Despoina Koumpouli [1], Varvara Koumpouli [2] and Antonios E. Koutelidakis [1,*]

[1] Unit of Human Nutrition, Laboratory of Nutrition and Public Health, Department of Food Science and Nutrition, University of the Aegean, Loforos Dimokratias 66, 81400 Myrina, Limnos, Greece; dkoub@hotmail.com

[2] Laboratory of Hematology, University General Hospital of Ioannina, Stavrou Niarchou Avenue, 455 00 Ioannina, Greece; vana_koumpouli@yahoo.gr

* Correspondence: akoutel@aegean.gr; Tel.: +30-225-408-3123 Fax: +30-225-408-3109

Abstract: The human gastrointestinal gut contains about 100 trillion of microorganisms including up to 5000 different types of bacteria called the "gut microbiome". Alterations in the composition of gut microorganisms (dysbiosis) can cause threatening for life diseases. This present seeks to evaluate if finally diet and more specifically functional foods affect the intestinal microbiome, and if obesity and the metabolic syndrome (Mets) are associated with the intestinal microbiome. This systematic review was accomplished according to PRISMA guidelines mostly using the key words functional foods, microbiome, obesity, Mets, Mediterranean diet. The search was carried out of recent scientific articles from the databases Pubmed, Scopus, and Google Scholar. The most studies discussed in this review showed a potential therapeutic effect of the Mediterranean diet rich in beneficial nutrients, on body weight, fat deposition, in correlation with modulation of the synthesis of gut microbiome. This literature review demonstrates a possible relationship between the metabolites of the microflora, the endotoxemia, obesity and Mets. The role of probiotics, prebiotics, and polyphenols in the prevention of obesity and Mets is of high importance in promoting healthy aging. The future challenge is to understand how different dietary patterns can regulate the composition of the gut microflora and whether these changes could be long-term.

Keywords: functional foods; microbiome; obesity; metabolic syndrome; polyphenols; prebiotics

1. Introduction

The human gastrointestinal tract contains approximately 100 trillion microorganisms, up to 5000 different species of bacteria that correspond to 5 million genes, weighing about 2 kg [1–4]. This population is different between individuals demonstrating the heterogeneity of human intestine microflora [5] and it is renewed every 3 days. Through competition for resources and colonization sites, they protect the host from colonization by pathogenic microorganisms [3,6,7]. The microorganisms that inhabit the human gut are called the "gut microbiome". Most of them form a symbiotic relationship with the host that is critical for many functions related to nutrition, metabolism, diseases, and normal functions of the human body. From birth, the gut microbiome is constantly evolving, while factors such as diet, lifestyle, age, and genetics, are very important for the microbial composition of the human gut [1].

The population of the gut microbiome mainly includes the bacterial phyla of Firmicutes (mainly genus Clostridia), Bacteroidetes (mainly Bacteroides), Actinobacteria and Proteobacteria [1,5,8]. Almost 90% of the human gut microbiome belong to only two phyla Firmicutes and Bacteroidetes [7].

The most widespread, non-communicable diseases such as obesity and metabolic syndrome are increasing worldwide. All are distinguished by a state of inflammatory disorder and are

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accompanied by changes in intestinal microflora. [5]. The World Health Organization (WHO) defines obesity as an excessive accumulation of body fat, mainly visceral fat, which can cause damage to health [9–12]. Worldwide, 2.1 billion people are overweight or obese [13]. The main concern about obesity is its association with chronic metabolic diseases such as insulin resistance, cardiovascular diseases, type II diabetes and MetS [9,10,14]. WHO defines MetS as a pathological condition characterized by obesity, insulin resistance, hyperlipidemia and hypertension [14,15].

Visceral obesity is associated with morbidity and complications of MetS due to the high production of inflammasomes cytokines and adipokines [2]. It has been shown that a diet with high fat and sugar content modifies the intestinal microbiome (at the level of phylum, genus and species), causing changes in metabolic pathways and induction of proinflammatory signals. Several studies have shown that dysbiosis is the cause of low-grade inflammation, obesity and consequently MetS [2,16].

Recent scientific research has linked the development of MetS with intestinal dysbiosis [14]. Intestinal dysbiosis increases intestinal permeability, resulting in translocation of lipopolysaccharide (LPS), a component of the external membrane of Gram-negative bacteria, thereby determining the metabolic endotoxemia which causes low-grade inflammation, resistance to insulin and weight gain [2,5,7,10,17–19]. The gut microbiota is considered the metabolic gateway between the external environment and the host, in terms of energy metabolism, body weight homeostasis and regulation of inflammation. Obesity has been shown to be associated with microbiome modification in the gut and obesity phenotypes are transmitted through gut microbiota in rodent models. The microbiome shares properties with both the environment and genes (it is hereditary and contains genetic material). Indeed, many researchers suggest that the microbial genetic material we have represents an extension of our genome, a "meta-genome" [10].

Diet is considered a key factor in changes in the microbial gut diversity. The main role of nutrition is to provide nutritional ingredients. Some food ingredients have beneficial effects in addition to the nutrition, introducing the concept of functional foods. Functional foods are those foods that offer benefits other from the basic diet when consumed as part of the regular diet [11] and they are defined as industrially processed or natural foods [20]. Numerous experimental studies have shown that the modification of the intestinal microbiome due to the consumption of functional foods causes beneficial metabolic effects such as decrease of LPS levels in the circulation and increasement of short-chain fatty acids (SCFA); The reduction of LPS levels leads to the reduction of local and systemic inflammatory processes while the increased SCFA levels are directly linked to increased satiety and consequent reduction of food intake [21]. Phenolics compounds and especially flavonoids are of particular interest because of their possible effect as antioxidant and anti-inflammatory compounds. Eating foods rich in flavonol has been shown to change the composition of the gut microflora, exerting prebiotic effects. In addition, the modification of the microflora contributes to improving insulin resistance, glycemic control, and glucose tolerance [11].

The aim of this literature review was to investigate the most recent scientific information about the relationship of diet and more specifically functional foods, probiotics, prebiotics and polyphenols with the modification of gut microbiome, the effects of gut microbiome to obesity and Mets, and more specifically if gut microbiome predisposes to their occurrence and what are the optimal eating habits for developing a healthy intestinal microbiome. The future challenge is to fully understand how different dietary patterns can modulate gut microbiota composition and whether these changes are long-lasting.

2. Materials and Methods

The literature search was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines via online academic search engines PubMed, Scopus and Google Scholar. The keywords used were “functional foods”, and “microbiome”, and “obesity”, or “metabolic syndrome”, or “polyphenols”, or “prebiotics”, or “Mediterranean diet”. The search was limited to research articles that were published in reviewed journals between 2014 and 2024 and that were written in English. From this research, 120 articles were studied and evaluated

 doi:10.20944/preprints202404.1427.v1

and the articles that included the specific keywords in their title or abstract were selected for further analysis. The selection criteria were primarily contemporary research, which was conducted in the last decade, and at the same time the analysis of nutritional and clinical studies, in which there was an evaluation of the influence of functional foods on obesity and Mets through their action on intestinal microbiome. Systematic reviews, articles in another language except English, articles with a year of publication before 2014, articles that did not include information about microbiome, functional foods in correlation with obesity and Mets, studies with unreliable study design and incompletely documented findings and evidence were excluded. Finally, 19article were selected for the literature review.

3. Results

3.1. Effects of the Mediterranean Diet on the Intestinal Microbiome, Obesity, and Metabolic Syndrome

In a recent study, 18 overweight/obese subjects and 18 normal weight controls followed Mediterranean Diet enriched with 40g/die High Quality-Extra Virgin Olive Oil for 3 months. Inflammation and oxidative stress were significantly reduced both in controls and in cases while IL-10 and adiponectin were increased in cases. Beneficial gut bacteria, mainly Lactobacillus strains, increased in cases after Mediterranean Diet enriched with High Quality-Extra Virgin Olive Oil [22]. In another study, 82 healthy overweight and obese subjects with a sedentary lifestyle, participated in a parallel 8 week randomized controlled trial. 43 participants followed a Mediterranean Diet and 39 maintained their regular diet. The dietary modifications in the group following the Mediterranean Diet led to reductions of carnitine in plasma and urine, in plasma cholesterol and increased *Faecalibacterium prausnitzii* and insulin sensitivity [23]. In 12-week single-arm pilot trial 9 participants followed nutritional counseling sessions according to Mediterranean Diet. The participants were men and women aged 40-80 years, nonsmokers, with type II diabetes and the results showed that bacterial variety increased after 4 weeks. Prevotella/Bacteroides ratio also increased and there was a reduction of glycated haemoglobin (HbA1c) at the end of study. There was an estimation of Alkaline phosphatase activity in fecal samples as a parameter of intestinal inflammation and intestinal permeability and was positively correlated with bacterial variability and negatively correlated with HbA1c [24]. Another transversal study investigated the association between the Mediterranean diet and gut microbiota in a group of 31 adults with non-declared pathology. The consumption of Mediterranean diet increased the population of Bacteroidetes, Prevotella and decreased the population of Firmicutes and Lachnospiraceae. Also, the Mediterranean diet increased the concentrations of faecal propionate and butyrate [25]. Table 1 summarizes the effects of the Mediterranean diet, in relation to the recent studies described previously.

Table 1. Summary results of the effect of Mediterranean diet on human microbiome.

Study Type	Study sample/Duration	Participants	Protocol	Summary of Results	Study Reference
Clinical trial	36 participants / 3 months	18 overweight/ obese subjects, 18 normal weight controls	Participants followed Mediterranean diet enriched with 40g/day HQ-EVOO	Mediterranean diet rich in HQ-EVOO leads to an increasementof Lactobacillus strains in Gut Microbiota	[22]
Randomized controlled trial	82 Subjects/8 weeks	82 overweight and obese Subjects	43 participants consumed a Mediterranean diet and 39 maintained their regular diets	Reductions of carnitine and plasma cholesterol and increased levels of Faecalibacterium *prausnitzii* and insulin sensitivity	[23]

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12-week single-arm pilot trial	9 participants/12 weeks	Men-women 40-80y, non smokers, with diagnosis of type 2 diabetes	Participants followed nutritional counseling sessions according to Mediterranean Diet	Increase of microbiota variety, Prevotella/ Bacteroides ratio increasement and reduction of HbA1c	[24]
Transversal study	31 participants	31 adults, 23 women, 8 men, 42y with non-declared pathology	Consumption of Mediterranean diet	Mediterranean diet increased the population of Bacteroidetes, Prevotella and decreased the population of Firmicutes and Lachnospiraceae	[25]

3.2. Effects of Probiotics on the Intestinal Microbiome, Obesity and Metabolic Syndrome

An interventional clinical trial studied the effects of the combination of a probiotic supplement of 30 g/day of carob and probiotic bacteria *L. helveticus, B. longum, S. Thermophilus, L. Lactis* on body composition and metabolic biomarkers in obese humans. 45 patients were randomly divided into three groups. A group of 15 people was called "diet only". Subjects were put on a low-calorie diet without any intervention. The second group of 15 people, called the "prebiotic group", followed the same diet but also received prebiotic supplements (2 carobs/day about 30g). And the 3rd group of 15 people called the "probiotic group" followed the same diet with additional probiotic supplements. The prebiotic and probiotic group showed a significant reduction in fat mass and insulinemia while the probiotic group showed a significant reduction in fasting blood glucose compared to the diet alone group [26]. A 3-week, randomized, double-blind, placebo-controlled, parallel pilot study investigated the influence of a low-calorie diet along with consumption of moderate-fat cheese containing the probiotic *Lactobacillus plantarum*. In this study 25 subjects consumed 50 g/day of probiotic cheese and 15 consumed the same amount of cheese without probiotics. In the probiotic group the body mass index (BMI) was significantly reduced compared to the control group. A positive correlation was observed between *Lactobacillus plantarum* colonization and the extent of reduction of morning diastolic blood pressure (BP) and morning systolic BP values. The hypocaloric diet together with the consumption of a probiotic cheese leads to a reduction of BMI and arterial blood pressure, both risk factors of MetS [27].

In a randomized study 51 patients with MetS were divided into two groups a control group of 25 subjects and a probiotic group of 26 subjects. The probiotic group had to consume probiotic-fermented milk for 45 days. In this study, beneficial effects of *B. lactis* on lipid profile, BMI and cytokine levels in patients with MetS were observed. A reduction of the pro-inflammatory cytokines Tumor Necrosis Factor (TNF-a) and Interleukin (IL-6) was observed, leading to an improvement of lipid metabolism and weight loss, contributing to the reduction of the characteristic parameters of MetS and obesity [28]. Another randomized, double-blind, placebo-controlled 8-week study evaluated the effects of consuming probiotic yogurt enriched with the probiotic strains *Lactobacillus acidophilus* and *Bifidobacterium lactis*. The 44 participants were randomly divided into two groups (22 in each group). Probiotic and regular yogurts contained *lactobacillus bulgaricus* and *Streptococcus thermophilus* while the probiotic yogurt was enriched with cultures of *B. lactis* and *L. acidophilus*. The probiotic yogurt group and the control group consumed 300 g/day of probiotic and regular yogurt for 8 weeks respectively. The probiotic yogurt group showed significant reductions in fasting glucose and insulin levels. In addition, the probiotic yogurt group resulted in significant reductions of vascular inflammatory markers for endothelial dysfunction that are elevated in MetS [29].

The aim of a randomized, placebo-controlled, double-blind intervention was to examine the effect of different doses of a multispecies probiotic supplement on LPS levels and cardiometabolic parameters in 81 obese postmenopausal women after 12 weeks of administration. The subjects were

 doi:10.20944/preprints202404.1427.v1

randomly divided into three groups that received a low or high dose of the supplement or a placebo. The probiotic group consumed 2 g of lyophilized powder of the probiotic mixture containing seven bacterial strains. The placebo group received the same sachets containing only the excipients, e.g., corn starch and maltodextrins. After 12 weeks of supplementation in both groups supplemented with high-dose and low-dose probiotics significant changes were found in the evaluated parameters, but not in the placebo group. High-dose probiotic supplementation for 12 weeks reduced LPS, waist circumference, fat mass, subcutaneous fat, total cholesterol (TC), triglycerides (TG), Low Density Lipoprotein (LDL), and glucose. The supplementation with low-dose probiotics modified the following parameters: waist circumference, fat mass, fat percentage, visceral fat, subcutaneous fat, TC, LDL. Probiotic supplementation improves the intestinal barrier, preventing the translocation of LPS into the circulation and ultimately leading to a reduction of inflammation [30].

Table 2 summarizes the actions of probiotics, in relation to the recent studies described previously.

Table 2. Summary results of Probiotic effects on obesity and Mets.

Study Type	Study sample/Duration	Participants	Protocol	Summary of Results	Study Reference
Prospective interventional study	45 obese patients/1 month	42 women, 3men /33-63 y.	Division of patients into three groups: low- calorie diet alone, prebiotic supplementation, probiotic supplementation	Prebiotic and probiotic groups significantly decreased fat mass, improvement of insulinemia in the prebiotic group compared to the diet- alone group and the probiotic group showed an improvement in fasting blood glucose compared to the diet group.	[26]
Randomized, double-blind, placebo-controlled, parallel pilot study	40 patients/3 weeks	30–69 years/ with Mets, obesity and arterial hypertonia (>130/85 mm Hg)	25 subjects ingested probiotic cheese and 15 ingested control cheese	The hypocaloric diet with the addition of a probiotic cheese reduced arterial BP, BMI and the risk of Mets in obese patients with hypertension.	[27]
A randomized trial.	51 patients with MetS/45 days	18- 60 years	Control group or untreated patients(n25) and a probiotic group (n26). The probiotic groups were required to consume 80 mL of probiotic milk containing B. *lactis ssp.*	*B. lactis* significantly ameliorated lipid profile, BMI and cytokine levels in patients with MetS.	[28]
A randomized, double-blind, placebo-controlled	44 patients/8 weeks	22 men and 22 women with MetS. 20 to 65 years old.	Participants were randomly divided into two groups a treatment or control group and consumed 300 g/d of	Consumption of probiotic yogurt ameliorated fasting blood glucose and improved endothelial function markers.	[29]

 doi:10.20944/preprints202404.1427.v1

clinical trial			probiotic yogurt containing Bifidobacterium lactis and Lactobacillus acidophilus or a regular yogurt for 8 weeks respectively.		
A randomized, placebo-controlled, double-blind intervention	81 participants/12-week	81 obese postmenopausal women	Division into three groups that received a placebo, a low dose, or a high dose of lyophilizate powder containing live multispecies probiotic bacteria.	There was an improvement of waist circumference, lipid profile, visceral fat, glucose metabolism, and LPS concentration in obese postmenopausal women	[30]

3.3. Effects of Prebiotics on the Intestinal Microbiome Obesity and Metabolic Syndrome

In a 12-week systematic randomized controlled trial the aim was to investigate the effect of prebiotic consumption on metabolic endotoxemia and systemic inflammation in overweight and obese adults. 37 participants were randomized into two groups. One group of 20 subjects consumed 7 g of oligofructose three times a day, and the second group of 17 subjects consumed an isocaloric maltodextrin placebo. Plasma LPS decreased by 40% in the oligofructose group while in the placebo group it increased by 48%. Oligofructose reduces metabolic endotoxemia and Plasminogen activator inhibitor (PAI-1) a risk factor for thrombosis. Higher levels of LPS and PAI-1 contribute to the complications of obesity, therefore consumption of prebiotics may help prevent obesity-related comorbidities [31]. Another triple-blind randomized controlled trial investigated the effects of inulin on inflammatory markers and metabolic endotoxemia in patients with type 2 diabetes. 49 diabetic women participated and were divided into two groups. An intervention group of 24 subjects and a control group of 25 subjects consumed 10 g/d inulin or maltodextrin for 8 weeks, respectively. In the inulin group, body weight and BMI decreased significantly, while in the maltodextrin group, remained unchanged. In the intervention group as opposed to the control group, energy intake and total fat were significantly reduced. Also, in the intervention group there was a significant reduction of fasting sugar, HbA1c, fasting insulin and a significant reduction of C-reactive protein (CRP), TNF-a and LPS. These results lead us to a conclusion that inulin supplementation modulates inflammation and metabolic endotoxemia in women with type 2 diabetes [32].

The aim of another randomized, placebo-controlled, double-blind, 6-week crossover trial was to investigate the prebiotic effect of inulin-type fructans on SCFAs and gut microbiota in patients with type 2 diabetes. Participants consumed 16 g per day of fructans inulin-type (a 50/50 mixture of oligofructose and inulin) and placebo (maltodextrin 16 g per day) along with their usual diet. Inulin-like fructans increased faecal SCFA concentrations without altering faecal microbial diversity. The results of this research show a modest potential of inulin-type fructans to improve gut microbiota composition and increase microbial fermentation in type 2 diabetes [33]. In a single center, double-blind, placebo-controlled trial conducted in 2 separate cohorts the aim was to evaluate the effect of prebiotic supplementation on gut microbiota, body composition, lipid profile, insulin concentrations and serum inflammatory markers, in otherwise healthy children with overweight and obesity. The participants were randomly assigned to either prebiotic oligofructose-enriched inulin or placebo control maltodextrin for 16 weeks. Subjects consumed either 8 g/day of oligofructose-enriched inulin or an isocaloric dose of 3.3 g/day of maltodextrin placebo. Supplementation with prebiotics significantly changed the synthesis of gut microbiota, and increased *Bifidobacterium spp* and normalized weight gain and reduced percent body fat and trunk fat [34].

Table 3 summarizes the effects of prebiotics, consistent with the above recent studies.

 doi:10.20944/preprints202404.1427.v1

Table 3. Summary results of Prebiotics effects on human microbiome related to metabolic diseases.

Study Type	Study sample/Duration	Partecipants	Protocol	Summary of Results	Study Reference
A randomized, double-blind, placebo-controlled trial	37 participants /12 weeks	Adults with overweight and obesity.	21 g of oligofructose or a maltodextrin placebo	40% reduction of LPS concentrations in the oligofructose group compared to a 48% increasement in the placebo group. PAI-1 reduced to a greater extent in the oligofructose group.	[31]
Triple-blind randomized controlled study	54 patients/8 weeks	diabetic females aged 20–65 years.	The intervention group consumed 10 g/d inulin supplement and the control group consumed similar amounts of maltodextrin	Inulin supplementation modulates metabolic endotoxemia and inflammation in women with type 2.	[32]
A placebo-controlled crossover study	25 patients (15 men) /6 weeks	Adult men and women with type 2 diabetes /41–71 y.	Consumption of 16 g of inulin-type fructans (a mixture of oligofructose and inulin) and 16 g placebo (maltodextrin) in a randomized order	Inulin-type fructans leads to moderate improvement of gut microbiota composition	[33]
Single-center, double-blind placebo-controlled trial	38 children /16 weeks	Male and female children, 20 in the prebiotic group and 18 in the control Group, aged 7–12 years with overweight or obesity	Supplementation of either oligofructose-enriched inulin 8 g/day or maltodextrin placebo once daily for 16 weeks	Consumption of Prebiotics normalized weight gain, ameliorated percent body fat and significantly modified gut microbial Composition enriching concentrations of *Bifidobacterium spp.*	[34]

3.4. Effects of Phytochemicals on the Intestinal Microbiome, Obesity and Metabolic Syndrome

In a randomized double-blind crossover trial, each patient consumed curcuminoids or placebo and then switched to the alternative regimen. Each treatment period was 30 days. 16 patients received curcuminoids 1 g/day for 30 days and another 16 patients received placebo for 30 days. Curcuminoids were administered in the form of capsules containing 500 mg of curcuminoids. This study showed that curcuminoid supplementation (1 g/day for 30 days) leads to a significant reduction of serum triglycerides [35]. The aim of a double-blind, placebo-controlled, crossover study was the effect of polyphenol-rich tomato extract on trimethylamine N-oxide (TMAO) and gut microbiota. 22 overweight and obese adults were divided into two groups and received 2150 mg of extract per day in one group or placebo (maltodextrin) in the other group for 4 weeks with a 6-week washout

 doi:10.20944/preprints202404.1427.v1

between interventions. The research extract significantly reduced urinary TMAO associated with gut microbiota composition [36]. In another double-blind, randomized, parallel-group, placebo-controlled pilot study, 28 obese men with MetS were studied over 35 days. Subjects were randomly divided into two groups to receive 1 g of trans-resveratrol orally twice daily or placebo while consuming a Western-style diet. In this study, the effects of trans-resveratrol, a natural product found in grapes, berries, and peanuts on insulin resistance in obese men with MetS were studied. The results showed an improvement of insulin sensitivity and a reduction of glucose concentration of 120 minutes in the oral glucose tolerance test. An increase of *A. municiphila* was also shown to be inversely associated with obesity and low- grade inflammation [37].

A randomized, placebo-controlled, double-blind, single-center study, middle-aged men between 30 and 60 years of age with MetS were randomized to either resveratrol or placebo treatment for four months. They received tablets containing placebo, low-dose resveratrol (75 mg twice daily) or high-dose resveratrol (500 mg twice daily). Changes were found in several metabolites in urine derived from essential amino acids, which cannot be synthesized by the body, however, the gut microflora may contribute to their production and degradation. Fermentation of these amino acids by colonic bacteria was found to produce phenols and indoles, which are excreted in the urine. Changes in urinary amino acids and derivatives revealed in this study suggest a resveratrol-induced regulation of gut microbiota in men with MetS [38]. Another double-blind, crossover, randomized, controlled clinical trial investigated the effects of olive oils, with different phenolic content, on urinary tyrosol (T) and hydroxytyrosol (HT) levels and LDL oxidation. The participants were 30 healthy non-smoking volunteers. The clinical trial of supplementation was conducted with three types of olive oils: refined, common, and virgin. After consumption of virgin olive oil, a reduction in LDL oxidation was observed in vivo. Increases in High Density Lipoprotein (HDL) and urinary T and HT were also observed [39]. In a 3-week double-blind, cross-over, randomized controlled trial, the objective was to evaluate the effect of daily consumption (60 ml) of high-polyphenolic extra virgin olive oil (HPOO), compared to low-polyphenolic olive oil (LPOO), on oxidative status and on inflammatory biomarkers. Olive oil polyphenols have many benefits for cardiovascular health due to their antioxidant and anti-inflammatory properties. Plasma total antioxidant capacity (TAC) is inversely related to chronic disease risks. The consumption of unrefined extra virgin olive oil with a high content of polyphenols led to a significant increase in the TAC of the plasma and a decrease in ox-LDL in the plasma [40].

Table 4 summarizes the effects of polyphenols in agreement with the above recent studies.

Table 4. Summary results of the effects of Polyphenols on human microbiome related to obese and Mets.

Study Type	Study sample/Duration	Participants	Protocol	Summary of Results	Study Reference
Randomized, double-blind, placebo-controlled, crossover trial.	30 Participants /30 days	18–65 y	Curcuminoids (1 g/day), or placebo.	Curcuminoid supplementation (1 g/day for 30 days) reduced triglycerides concentrations in serum	[35]
A double-blind, placebo-controlled, cross-over study	22 participants /4 weeks	Overweight and obese adults.	2150 mg of a water-soluble tomato extract rich in polyphenols per day or placebo (maltodextrin) for 4 weeks with a 6-week	Significantly reduced urine TMAO, related with changes in microbial composition.	[36]

 doi:10.20944/preprints202404.1427.v1

			wash-out between interventions.		
A double-blind pilot randomized parallel group design placebo-controlled study	28 participants/35-days	Obese men with MetS	Resveratrol 1 g orally twice daily or placebo while consuming a western-style diet	Improvement in insulin sensitivity and glucose tolerance	[37]
A randomized, placebo-controlled, double-blinded, single-center study.	66 participants/ 4 months	Male gender,30-60 y, and MetS.	Randomized to either resveratrol or placebo treatment	Urinary derivatives of amino acids, which reflect the synthesis of the gut microbiota, were altered after resveratrol treatment.	[38]
Double blind, cross-over, randomized, clinical trial	30 healthy non-smoking volunteers/ 3 weeks	Adults/both male and female	Common, virgin, and refined olive oils were sequentially consumed over three periods of 3 weeks	Reduction in vivo of LDL oxidation and increasement of T and HT in urine	[39]
Double-blind cross-over trial	43 participants/3 weeks	20 -70 y, 66% females,44% of study participants were overweight and 4% were obese	60 mL/day of HPOO (320 mg/kg polyphenols) or LPOO (86 mg/kg polyphenols) for three weeks.	Significant reduction of ox-LDL and CRP in plasma and increase in the TAC of the plasma	[40]

4. Discussion

The prevalence of obesity is increasing worldwide, reaching pandemic proportions, causing significant effects on health and the economy in general [41]. The present literature review according to the above human studies clarifies the correlation between nutrition and more specifically functional foods, with the modification of the intestinal microbiome, shows that obesity and Mets are linked to the intestinal microbiome, that gut microbiome predisposes to their occurrence and indicates which are the optimal nutritional habits to develop a healthy gut microbiome [14].

The gut microbiota plays a key role as a regulator of energy homeostasis and fat deposition, acting as a mediator be-tween host and environmental factors. The gut microbiota composition of obese individuals is different from that of normal individuals, and the association of dysbiosis with obesity and related metabolic diseases has been demonstrated by both animal and human studies [10,16]. However, remains unclear which components of the gut microbiota are the cause of weight gain and abnormal glucose and fat metabolism, and which are protective against obesity and metabolic disorder; thus, these are still under investigation. A relationship between microbiota metabolites, endotoxemia and MetS is clearly emerging. Recent findings have shown that some microorganism derived metabolites (including TMAO, LPS) induce sub-clinical inflammatory processes involved in obesity and MetS [9].

Among the factors influencing the composition of gut microbiota, dietary habits play a key role [5,6]. Certain dietary patterns are more effective than others in modifying the gut microbiota. In particular, the Mediterranean diet rich in beneficial nutrients and bioactive compounds, probiotics,

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prebiotics and polyphenols are particularly effective in regulating the composition of gut microflora and inflammatory processes and subsequent endotoxemia [42]. Gut microbiota is associated with the production of SFCA that can bind to their receptors G protein-coupled receptors, GPCR-41 and GPCR-43 leading to the secretion of glucagon-like peptide 1 (GLP-1). GLP-1 in-creases energy expenditure, reduces food intake, improve glucose metabolism and insulin secretion, and ameliorates intestinal barrier function [5,18,43]. So, there is a decrease of translocation of bacteria and LPS, which increases anti-inflammatory parameters and reduces proinflammatory markers and HbA1c. To analyze intestinal inflammation and permeability, Alkaline phosphatase (ALP) activity from fecal samples can be determined. Intestinal ALP is very much related to diet. Following a Mediterranean type of diet increases the activity of intestinal ALP. The activity of this enzyme is related to an increasement of bacteria variety and a reduction of HbA1c. This can be attributed to the ability of intestinal ALP to reduce the inflammation by altering gut microbiota synthesis and to dephosphorylate LPS reducing intestinal permeability and in-creasing insulin sensitivity [24].

A Mediterranean-type diet is associated with a different microbiome than that of a Western-type diet. The microflora, associated with a Mediterranean-type diet, presents greater diversity (a greater number of bacterial species), which has a positive impact on human health. Following a Mediterranean-type diet is protecting against dysbiosis, and is associated with increased SCFA levels, decreased TMAO levels, and abundance of fiber-degrading Prevotella and Firmicutes [2,42]. In contrast, the Western diet leads to the reduction of specific bacterial strains, thus negatively affecting several metabolic functions. Diets with an abondance in fat and sugar components may alter intestinal microflora causing modifications responsible for obesity and Mets [2,5,44].

Mediterranean Diet is rich in functional foods, beneficial nutrients and bioactive compounds, probiotics, prebiotics and polyphenols is a healthy type of diet that reduces the risk of obesity and Mets [44,45]. The several studies discussed above have shown potential therapeutic effects of functional foods on body weight, BMI, waist circumference, fat deposition, lipid profile, modulation of the synthesis of gut microbiome and chronic inflammation status [30,34]. One of the main constituents of Mediterranean Diet, is Extra Virgin Olive Oil that has a very important beneficial role due to oleic acid and to polyphenols, that has an antioxidant activity [22]. Obesity, Mets and inflammation are shown to be related to nutrition disorders and the most recent bibliography indicates that gut microbiome has a very important role both in disease development and in wellness [16].

5. Conclusions

This literature review demonstrates a relationship between the metabolites of the microflora, the endotoxemia, obesity and Mets. The role of functional food, probiotics, prebiotics, and polyphenols in the prevention of obesity and Mets is very much important in promoting healthy aging. The future challenge is to understand how different dietary patterns can regulate the composition of the gut microflora and whether these changes are long-term.

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