

Review

The role of Mediterranean diet and gut microbiota in type-2 diabetes mellitus associated with obesity (diabesity)

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Keywords

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Summary

The human body is made up of 10^{14} human cells and 10^{15} bacterial cells, forming a combined structure that is described as a "superorganism". Commensal, symbiotic, and pathogenic microorganisms in the human body, many of which are located inside the intestine, affect health conditions and diseases. An important factor contributing to the development of chronic diseases is dysbiosis, which occurs when the number of pathogenic microorganisms increases. Dysbiosis is associated with increased intestinal permeability, endotoxemia (increased LPS), pro-inflammatory cytokine release, energy harvest, and adiposity, thus being involved in the pathogenesis of disorders like diabetes and obesity. Nutritional habits are the most important environmental factor that affects intestinal microbial composition. A dietary pattern that was proven successful in regulating gut microbiota is the renowned Mediterranean diet, which is characterized by high plant-based foods consumption, moderate fish and dairy products consumption, and low red meat consumption. There is an inverse relationship between adherence to the Mediterranean diet and chronic diseases like obesity and diabetes. In addition to the direct effects of the Mediterranean diet on the pathogenesis of these diseases, it can also be effective in preventing these diseases due to its effects on the intestinal microbiota. It is noted that the number of Bifidobacterium and Bacteroides increases the longer one's eating habit adhere to the Mediterranean diet, and the number of Firmicutes decreases, accordingly, thus supporting the symbiotic distribution in the intestinal microbiota.

Introduction

Relman and Falkow reawakened the project named "second human genome project", in 2011. This project attracted attention to the necessity to analyze the microbial genome in the determination of microbial colonization in the gastrointestinal (GI) system. Hence, it provided knowledge about endogenous flora in GI and its differences in disease and health status [1]. There are about 10^{1}⊠ bacterial cells in the human body. Along with bacteria, other microorganisms, viruses, and archaea use the human body as a host and can be found in different anatomical parts of the body such as skin, urogenital region, respiratory tract, oral cavity, digestive system etc. Amongst the different regions of the body; the digestive system possesses a large part of the microbiota within the human body [2, 3]. All the anatomical parts of the digestive tract, from mouth to anus are involved in digestion and absorption processes. Also, commensal bacteria colonized in the digestive tract is a modulator for the host's health via influencing different physiological processes and gene expressions. Nutritional habits are the most important environmental factor that affects the gut microbiota composition [4]. It is emphasized in the literature that the Mediterranean diet model supports the composition of the gut microbiota for the benefit of human health [5]. The Mediterranean diet model is described as one of the plant-based nutritional models. The traditional Mediterranean diet model involves rich consumption of vegetables, beans, nuts and seeds, fruits, whole intact grains, fish and other seafood; olive oil, and dairy products (mainly yoghurt and cheese). Whereas on the other hand, it involves low consumption amounts of red meat; sugars or honey and low to moderate consumption amounts of wine [6].

Food environment, diet and physical activity are some of the significant players in the development of diabetes and obesity [7]. Both of the diseases are in the characteristics of an epidemic according to the global drastic increase in their prevalence [8]. According to World Health Organization (WHO) statistics 2021, 463 million people were diagnosed with diabetes and 650 million people were diagnosed as obese, worldwide [8, 9]. Type-2 diabetes is more frequent than Type-1, such that 95% of all diabetes are diagnosed to be Type 2. A range of complications including Type-2 diabetes, arthritis and cardiovascular disease (CVD) are related to obesity. The reasons behind this consist of the building of excess adipose tissue, insulin resistance and chronic inflammation. Noninsulin-dependent diabetes, namely Type-2 diabetes is a frequent condition found in obese individuals. Recently, a new unique term referred to as "diabesity" is used to describe the situation

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of Type-2 diabetes mellitus associated with obesity [10]. WHO states that Type-2 diabetes and obesity are the two preventable pathological disorders. In these cases, modifiable risk factors such as dietary habits and physical activity are effective in both its prevention and management [9, 11]. Epidemiological studies have revealed that the Mediterranean diet has a positive effect on preventing both obesity and Type-2 diabetes [12, 13].
The Mediterranean diet directly interacts with diabesity and the gut microbiota. In this chapter, the interaction between the Mediterranean diet, Type-2 diabetes - obesity (diabesity) and gut microbiota will be studied.

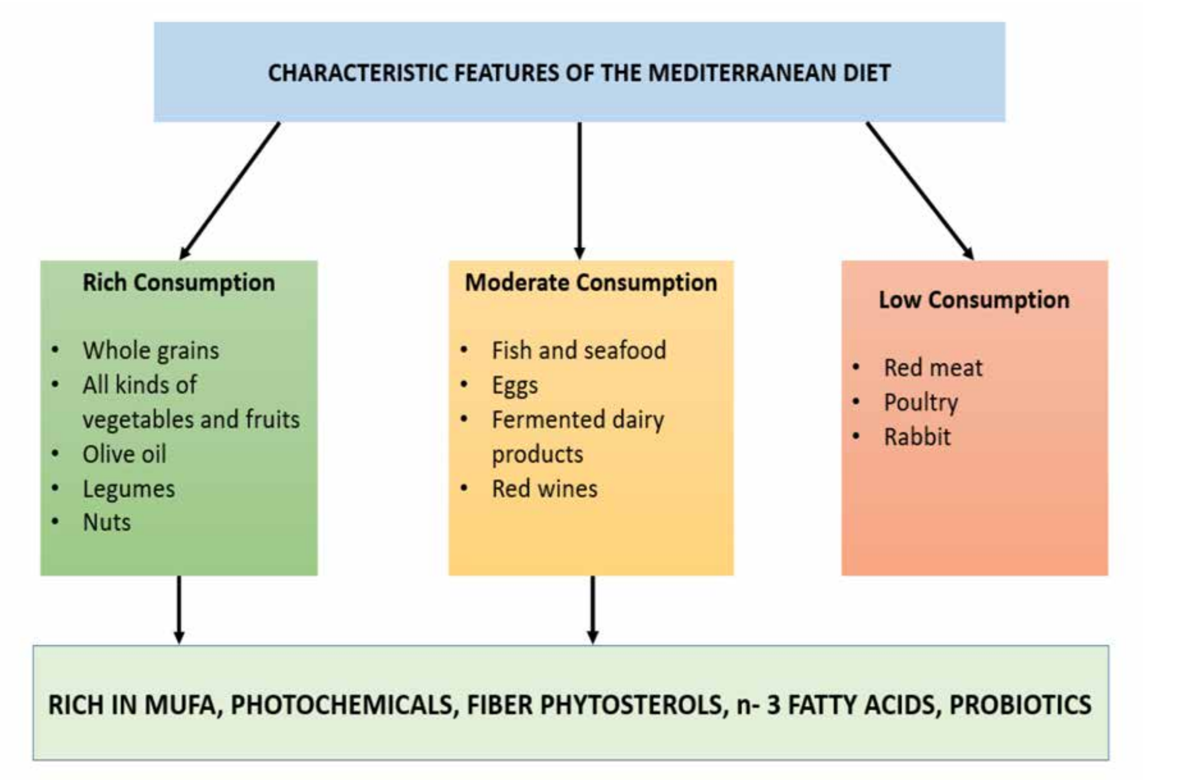
Definition and components of the mediterranean diet model

The Mediterranean diet reflects the taking of balanced and adequate nutrients (carbohydrate, protein, fat, vitamins and minerals) which are rich in plant-based proteins, complex carbohydrates and fiber, monounsaturated fatty acids (MUFA) (n-9) and polyunsaturated fatty acids (PUFA) (n-3) and poor in animal-derived foods. Thus, it positively affects the prevention and management of non-communicable chronic diseases [14, 15]. Figure 1, represents the Mediterranean diet model. This eating model is also environmentally and sustainability friendly, since it involves the consumption of seasonal and local foods [16].
Balanced nutrition and food diversity are the key players in protecting and maintaining a healthy life. Each food group contains different nutrients and bioactive nutrients. The Mediterranean diet is an eating pattern that provides all the food diversity that fulfils the nutritional requirements and keeps the consumers healthy [18, 19]. Nutrient/non-nutrient components are found in high amounts in plant-derived foods and flavouring spices. Consuming these foods known as containing bioactive nutritional components has a potentially positive effect on human health. The Mediterranean model recommends for consumption of high amounts of bioactive food components [20, 21].
Due to the food groups involved; this model also recommends a high to moderate daily consumption of MUFA, PUFA, phytochemicals, fiber, phytosterols and probiotics [22]. The bioactive nutrient components of the Mediterranean diet and its correlation of potential positive effects on health are summarized in Table I.

Gut microbiota

Microbiota is defined as a community of microorganisms living on/in the host whereas microbiome is the entire genome of the microbiota [28]. In a healthy state of the human body, in the concept of microbiota, commensal, symbiotic and pathogenic microorganisms are living within the body in a homeostatic fashion. The balance of the microbiota composition is a key determining factor for the disease and health conditions of the host.

Fig. 1. Mediterranean diet model: Consumption distribution of some food products in the Mediterranean diet (The figure has been created in PowerPoint using the information in [14, 16, 17]).



Tab. I. Bioactive component of Mediterranean Diet (MD).

Component of MD	Bioactive food component/s	Reference(s)
Olive oil	Hydroxytyrosol, Tyrosol, Oleuropein, Oleocanthal, Oleacein, oleic acid.	[23]
Fruits and Vegetables	Carotenoids, Quercetin, Fiber, Vitamin A- C- E, Folate, Se, Lycopene etc.	[17]
Red wine	Resveratrol, Quercetin	[24]
Fish	n- 3 fatty acid	[25]
Seeds	Linolenic acid, vitamin E	[17, 26]
Culinary Herbs and Spices	Quercetin, Securenet, Rosmarinic acid, Chlorogenic acid, Davidigenin	[27]
Dairy products	Calcium, vitamin D, linoleic acid, lactoferrin, lactic-acid-producing bacteria	[24]

There are 10% human and 90% bacterial cells within the human body. This composition together is called the superorganism, with optimal living status [29]. Microbial content varies throughout life in response to environmental and non-environmental factors and is host-specific [30]. Symbiont and pathobiont indicate a balanced distribution in the microbiota of healthy individuals. Dysbiosis is defined as the deterioration of the balance between the symbiont and the pathobiont composition and the increase in pathogenic microorganisms [31]. The most important factors that affect microbial composition can be summarized as phenotype, age, type of birth delivery, physical inactivity, smoking, alcohol consumption and dietary habits [32]. In recent years, the scientific world has focused on studies to clarify the role of gut microbiota in health and diseases. It is believed that the development of dysbiosis causes an increase in intestinal permeability, endotoxemia, energy production (energy harvest), adiposity and pro-inflammatory cytokine production. Thus plays a role in the etiopathogenesis of diseases such as CVD, obesity, diabetes, some cancer types, rheumatoid arthritis, and non-alcoholic fatty liver disease, which are based on systemic inflammation [33, 34]. The human gut microbiota, constitutes 10-100 trillion microbial cells making the largest symbiotic relationship within the host [35].

As well as maintaining intestinal homeostasis, gut microbiota also influences the metabolism, physiology, and immune function within the host [34, 36]. Although, the composition of gut microbiota has a very rapid turnover; in terms of species composition it is fairly stable [37]. Its composition consists of more than 500 species within 6 phyla which are *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria* and verrucomicrobia. Of these bacterial population, 90% accounts for *Bacteroidetes* and *Firmicutes*. On the other hand, proteobacteria and *Actinobacteria* and other pylas of verrucomicrobia, *Cyanobacteria*, *Fusobacteria*, *Spirochaetes*, are scarce compared to *Firmicutes*, *Bacteroidetes* in the colon [38, 39]. Several human diseases are associated with the *Fusobacterium*. Hence, it is generally considered as a pathogenic bacterium. Also, *Firmicutes* and proteobacteria are considered as pathogenic since they negatively affect the glucose and fat metabolism within the gut. In contrast, verrucomicrobia, *Actinobacteria*, and *Bacteroidetes* influence gut health positively by providing a host to become resistant to infectious disease, involving in glucose homeostasis and generation of the short-chain fatty acids (SCFAs) which are known to decrease inflammation [38]. Symbiotic or dysbiotic distribution of intestinal microbial distribution is closely associated with increased disease risk or optimal health. Studies have shown that symbionts such as *Bacteroidetes thethaiotamicron, Bifidobacteria, Lactobacilli, and Faecalibacterium prausnitzii* are dominant in the symbiotic microbiota, while pathobionts such as *Bacteroides spp., Clostridium difficile* are dominant in the dysbiotic microbiota [32]. A dysbiotic distribution of the gut microbiota is closely related with:

- increased intestinal permeability;
- increased endotoxemia (increased LPS production);
- increased pro-inflammatory cytokine secretion;
- increased adiposity;
- increased insulin resistance;
- increased energy harvest.

There is a positive correlation between dysbiosis and increased risk of inflammatory disease due to these metabolic changes [4, 40].

As mentioned earlier, dietary habits are one of the important environmental risk factors that affect microbiota composition. For this reason, recent studies have focused on studies related to gut microbiota - healthy nutrition habits - and decreased prevalence of chronic diseases.

Triple interaction; Gut Microbiota - Diabesity- Mediterranean Diet

Obesity is defined as the increase of adipose tissue in the body to a degree that impairs health [9]. Also, it is the most important risk factor contributing to the development of Type-2 diabetes [41]. Studies have shown that approximately 80% of individuals with Type-2 diabetes are obese. This close relationship between Type-2 diabetes and obesity is related to the lipid overflow, inflammation and adipokine hypothesis. The pathological condition consisting of the combination of these two diseases is called diabesity [10]. According to this hypothesis, a high serum concentration of free fatty acids (FFA) causes increased oxidative stress on pancreatic β-cells and both β-cell apoptosis and defects in insulin receptor signalling. Moreover, the insulin signalling pathway is inhibited by the products of fatty acid metabolism such as diacylglycerols (DAGs), long-chain acyl-CoA esters (LCAEs) and ceramides. It is argued that adipocytokine levels increases due to increased adipose tissue causing the antilipolytic activity of insulin to be inhibited, as well as the coexistence of lipotoxicity and glucotoxicity [10]. The components of the Mediterranean diet described in the previous section (See: Title 2) affect the composition

Tab. II. Effects of Mediterranean Diet Model versus Western Diet Model on Microbial Diversity.

Diet Type	Metabolic Effect	Microbiota Diversity
Adherence to Mediterranean Diet [54, 55]	↓ Oxidative stress, inflammation, immune system function, Endotoxemia, a pro-inflammatory cytokine, Obesity, Type 2 Diabetes Mellitus	↑ *Bacteroides, Lactobacilli, Bifidobacteria, Roseburia* ↓ *Firmicutes, proteobacteria*
Adherence to Western Type Diet [32]	↑Oxidative stress, inflammation, immune system function, Endotoxemia, a pro-inflammatory cytokine, Obesity, Type 2 Diabetes Mellitus	↓ *Bifidobacterium, Eubacterium* ↑ *Firmicutes*

of the gut microbiota. Adaptation to the Mediterranean diet has the potential to prevent the development of obesity and type 2 diabetes by increasing the diversity of the intestinal microbiota and modulating its composition (increased *Bacteroidetes, Lactobacilli*, *Bifidobacteria*, *Faecalibacterium* and decreased *Firmicutes*, proteobacteria). These changes lead to increased microbiota-mediated metabolites, intestinal homeostasis, decreased dysbiosis and decreased intestinal permeability [42].

The role of the microbiota undoubtedly is a key determinant in diabesity. Many animal studies have revealed that gut microbiota composition in healthy individuals compared to diabesity is different [43]. Studies have shown that obese and type 2 diabetic individuals have lower microbial diversity compared to healthy individuals, as well as an increase in the number of *Firmicutes* and a decrease in the number of *Bacteroidetes* [43, 44]. Symbiotic change in the dysbiotic microbial composition of individuals diagnosed with obesity and type 2 diabetes draws attention as a potential treatment method for improving diabesity-related biomarkers. *Sergeev et al.*, revealed that individuals diagnosed with obesity and type 2 diabetes after prebiotic and galacto oligosaccharide supplementation were affected in parameters such as HbA_{1c}, waist circumference, BMI and body weight in parallel with the abundance of *Bifidobacterium* and *Lactobacillus* in their intestinal microbiota [45].

Effects of Mediterranean Diet Model on Gut Microbiota

The potential positive effects of the Mediterranean diet on health are well established. Furthermore, increased adherence to the Mediterranean diet has been associated with the suppression of the growth of pathobionts such as proteobacteria and *Bacillaceae* phyla. Whereas on the other hand promotes the growth of *Bacteroidetes* and beneficial *Clostridium* species in the intestinal microbiota through Mediterranean diet components (MUFA, PUFA, polyphenols, phytosterols and fiber). In contrast to the western-style diet, the Mediterranean diet model (Tab. II) decreases the *Firmicutes*: *Bacteroidetes* in the gut supporting the prevention of chronic diseases such as Type-2 diabetes, obesity, CVD and cancer [46, 47]. There is an inverse relationship between the consumption of MUFAs and PUFAs and the prevalence of diseases such as obesity, Type-2 diabetes, CVD, cancer and hypertension [48, 49]. In addition, high amounts of MUFAs and PUFAs consumption can modulate human health by affecting intestinal microbial composition. It has been reported that MUFAs have a potentially positive effect on the intestinal microbiota by supporting the growth of Lactic acid-producing bacteria (*Bifidobacterium* and *Lactobacillus*) [46]. Similarly, PUFAs can positively affect the intestinal microbiota and human health via a potential suppressive effect on the growth of *Enterobacteria* and support the growth of *Lachnospiraceae* and *Bifidobacteria* and modulate the *Firmicutes*: *Bacteroides* ratio [50]. There is a bidirectional relationship between polyphenols and microbiota, bioactive nutritional components commonly found in vegetables and fruits and one of the main components of the Mediterranean diet, due to the conversion of polyphenols to metabolites that positively affect human health by colonic bacteria and the effects of these metabolites on the colonic microbiota [51]. Effects of polyphenols on microbiota composition: I) stimulating the growth of beneficial bacteria living in the colon, II) inhibiting pathogenic bacteria growth, and III) having positive effects on enterocyte development and integrity [52]. In the study conducted by *Wang et al.*, it was reported that the number of *Bacteroides* increased after the red wine polyphenol resveratrol supplementation, and the symbiotic distribution was supported by this effect [25]. According to *Etxeberria et al.*, the supplementation of quercetin, which is common in vegetables and fruits, causes a change in the composition of the intestinal microbiota. This change was reported as decreasing the *Firmicutes/Bacteroidetes* ratio and inhibiting the growth of bacterial species (*Erysipelotrichaceae, Bacillus, Eubacterium cylindroides*) that contribute to the development of obesity [53].

Due to the positive potential effects of polyphenols on the intestinal microbiota composition, studies on this subject need to be continued to provide more precise statements about their potential to be used in the treatment and prevention of Type-2 diabetes and obesity through reduced endotoxemia and inflammation.

Conclusion

The gut microbiota plays an important role in body homeostasis; such that it can modulate, the enteric nervous system and central network system via producing neurotransmitters. Hence the link between human microbiota and diet has led to the development of a "second brain" reputation. Undoubtedly, a bidirectional communication network – the "gut-brain axis" is a bridge between the enteric and central nervous systems [56]. Also, the habit of consuming an unhealthy diet in a way of not favouring the microbiota in the gut is associated with many diseases such as diabetes and obesity; which was the main subject of this chapter. Thus, to keep the gut microbiota healthy consuming a healthy diet such as the Mediterranean diet is significant - and within the scope of the "second brain" reputation, it is not wrong to state that "you are what you eat".

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Conflicts of interest

The authors declare no conflict of interest.

Author's contributions

S.O.and N.S. have written the chapter under the supervision of T.S. All authors have contributed on literature research. Figure 1 in the manuscript have been designed by S.O. and proofread has been done by N.S. Design of the study have been conducted by T.S.

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