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

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Summary
The human body is made up of $10^{13}$ 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 $10^{13}$ 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 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
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, mod-
ifiable risk factors such as dietary habits and physical
activity are effective in both its prevention and manage-
ment [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 interacts with diabesity and the
the gut microbiota. In this chapter, the interaction
between the Mediterranean diet, Type-2 diabetes - obe-
by (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 (MU-
FA) (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 nutri-
ents. 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 recom-

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]).

Gut microbiota
Microbiota is defined as a community of microorgan-
isms living on/in the host whereas microbiome is the en-
tire genome of the microbiota [28]. In a healthy state of
the human body, in the concept of microbiota, commen-
sal, 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.
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 intestin permeability, endotoxiaemia, 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 pylon 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* thetaiotamicron, *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 endotoxiaemia (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 - DIABETES - 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 (DGAs), 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

| Component of MD | Bioactive food component/s | Reference(s) |
|-----------------|---------------------------|--------------|
| Olive oil       | Hydroxytyrosol, Tyrosol, Oleuropein, Oleocanthal, Oleaein, 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, Securenert, Rosmarinic acid, Chlorogenic acid, Davidigenin | (27) |
| Dairy products | Calcium, vitamin D, linoleic acid, lactoferrin, lactic-acid-producing bacteria | (24) |
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 diabetes. Many animal studies have revealed that gut microbiota composition in healthy individuals compared to diabetics 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 diabetes-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 HbA1c, 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 Bacilliaceae phyla. Whereas on the other hand promotes the growth of Bacteroidetes and beneficial Clostridiaceae 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 MUFA and PUFAs and the prevalence of diseases such as obesity, Type-2 diabetes, CVD, cancer and hypertension [48, 49]. In addition, high amounts of MUFA and PUFAs consumption can modulate human health by affecting intestinal microbial composition. It has been reported that MUFA 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 Etcheberia 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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