The impact of the Mediterranean diet on gut microbiota in diabesity

by

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Abstract

Diabetes and obesity are currently some of the most prevalent chronic conditions and are still growing globally. These conditions are accompanied by modifications in the gut microbiota in connection to specific dietary patterns. This report aims to review the research into the human gut microbiota in connection to the Mediterranean style diet of type 2 diabetes mellitus associated with obesity. Current research has revealed that the gut microbiota differs in lean versus obese people, as well as individuals who have type 2 diabetes and people who do not. To comprehend the change of gut microbiota in obesity and type 2 diabetes, it is important to first understand the mechanisms that regulate the gut microbiota composition. During the early stages of life, several aspects affect the gut microbiome. Some of these aspects include the mode of delivery, if breastfeed or formula-fed, level of prematurity of the child, and antibiotic use. From the time a child is introduced to table foods, the gut microbiome is affected by dietary nutrient composition. There have been new and ongoing research on the role of gut microbiota in obesity and diabetes concerning dietary intake. Results showed that a Western-style diet promotes a gut microbiota which tends to promote obesity, whereas the Mediterranean style diet has beneficial influence on the gut microbiota, so it may be considered for use in clinical management and prevention in diabesity. This could indicate that specific dietary interventions may favorably affect metabolism due to the change in gut microbiota composition. Potential causes of this beneficial effect of the Mediterranean style diet on the gut microbiota in diabetes and obesity has been attributed to an increase in non-digestible dietary fibers resulting in the increased production of short-chain fatty acids through fermentation and increased probiotic intake, leading to an overall reduction in gut dysbiosis with an improvement in insulin resistance. Additionally, some research found a connection between the gut microbiome and the level of

activity in the energy and glucose metabolism effect on the endocannabinoid systems. Thus, the purpose of this report is to determine the connection the impact nutritional components of the Mediterranean style diet have on the gut microbiota in individuals with diabesity and to understand and create awareness of the influence the diet has over these possible key components.

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Acknowledgments

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Introduction

The gut microbiome, termed in 2001, by the biologist Joshua Lederberg, is the entirety of all microorganisms including the genetic material in the human intestine. [1] The intestinal gut microbiome, also interchangeably termed as the microbiota, is a lively combination of microbes that develop under the influence of genetics, diet, environment, and disease. Trillions of microorganisms exist in the human gastro intestinal tract and create a multifaceted ecological system that functions as its own organ. [2] The gut microbiota of the gastro intestinal tract is comprised of commensal, symbiotic, and pathogenic microorganisms. Commensal microorganisms refer to bacteria that induce protective responses within the host's immune system and prevent the colonization and invasion by pathogens, where symbiotic microorganisms are bacteria that exist in symbiosis with each other or another organism. [3] Most bacteria in the human body are found in the gastrointestinal tract, from the mucosa to the lumen where they are in direct contact with chyme. [4] The small intestine is comprised of the duodenum, jejunum, and ileum. The small intestine is the primary site for digestion of foods and nutrient absorption. The large intestine consists of the cecum, colon, rectum, and anal tract. The large intestine is the site of bacterial fermentation of the remaining carbohydrates, absorption of final vitamins, and excretion of feces.

The profile of the bacterial population varies depending on the location in the gastrointestinal tract as well as each individual person. The combined population of microbiota in the human body accounts for 35% to 50% of the volume of the colonic contents with thousands of different species. [4] [5] The relationship between the human host and the gut microbiota is interdependent. The main roles of the commensal gut microbiota comprise the production of important mucosal vitamins and the production of metabolites such as short-chain fatty acids which stem from the colonic fermentation of non-digestible polysaccharides and provide energy. [5] Additionally, the gut microbiome is responsible for protection from pathogen colonization, cell proliferation of the epithelial cells, development of the immune system, and development of the gut-brain axis. [1] Further, the gut microbiome is involved in the metabolism and conversion of bile acids, and carbohydrate and amino acid transport. [6]

The development of the gastrointestinal tract begins as a fetus in utero through the amniotic fluid and is affected by the form of birth and if the infant was breastfed or formula-fed. [7] Research showed that human breastmilk is high in beneficial Bifidobacterium which may promote the development of healthy gut microbiota in infants. [6] The newborn gut microbiome has shown to be compromised of only a few species but rapidly increases in variety within the first few years of life. [8] While the reasons are still unknown, it is suspected to be due to intestinal surface growth, environmental bacterial exposures, and dietary changes. [1] When the diet in the early years of life is advanced from simple solid foods to more complex polysaccharides, the gastrointestinal tract changes from an unstable environment to a more constant microbiota. Further, research has revealed that the gut microbiota acclimates in accordance to the foreign diet of the hosts, depending on the geographical location, adapting bacteria from that specific environment. [1] The gut microbiome's main characteristics of complexity and stability are affected differently in health versus disease, from infancy to older age. [7]

Numerous aspects can impact the gut microbiota throughout microbiome growth, such as genetics, medication, stress, exercise, and diet. [9] Even though some of these factors may be beneficial, others have a negative impact on the complexity and stability of the microbiota. These negative factors can possibly introduce microbial dysbiosis which disrupts the delicate symbiosis between gut microbiota and host. [7] The term dysbiosis refers to a change or reduction in the abundance of relative proportions of these beneficial bacteria and has been associated with various diseases. [4] This imbalance of the gut microbiota may lead to an increase in negative bacteria in the gastrointestinal system of the host and comes with the development of oxidative stress and inflammation, which is associated with several autoimmune and metabolic diseases, including inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, cancer, obesity, and type 2 diabetes mellitus. [4] The high fat "Western-style" diet has been linked to growth of undesirable gut bacteria which may undesirably impact the microbe community in the gut microbiota. [7]

These days, diabetes and obesity are some of the most prevalent chronic conditions and are still growing globally. According to the Center for Disease Control's 2020 National Diabetes Statistics Report, 34.2 million Americans have diabetes, of whom 89% are also overweight or obese. [10] Diabetes mellitus type 2, heart disease, and cancer are the main chronic conditions and causes of death and disability in the United States. [11] Type 2 diabetes is characterized by hyperglycemia, resulting from insulin resistance on the cell receptors of the muscle tissues, and decreased insulin secretion capacity from a deficiency of pancreatic beta-cell function. [12] Risk factors for developing type 2 diabetes mellitus include family history, ethnic background, physical inactivity, and obesity. [12] However, obesity and being overweight do not just present a risk for the development of type 2 diabetes but are also an increased factor in diabetes-related complications. [10] This shows that obesity and type 2 diabetes mellitus are interrelated not only in the development but also the progression of disease.

Being overweight, obese, and physical inactive are considered modifiable risk factors for type 2 diabetes. Obesity is defined as a body mass index (BMI) of 30 kg/ m^2 or higher. [10]

Obesity occurs as a result of imbalanced total energy intake from food and beverages and total energy expenditure, which includes a sedentary lifestyle. Previous research has shown a possible connection between the diabetes and obesity and the type of diet, where the Western-style diet may be detrimental and the Mediterranean diet may be beneficial. The Mediterranean diet has been studied extensively and was found to drop mortality rates by 70% in patients with chronic disease. [13] Thus, the purpose of this report is to review and assess the significance of the relationship between the impact of a specific diet and nutrition interventions on the gut microbiota as it relates to the chronic disease of type 2 diabetes with obesity.

Review of the Literature

Gut Microbiota

Obesity and type 2 diabetes develop in an entwined multifaceted process that involves genetic predisposition and environmental factors. In the past, science has attempted to reveal the details of these influences and discovered the increasing importance of the gut microbiota connecting genetics, immune system, environment, and diet with diabesity. The gut microbiota is defined as a specific type of microorganisms living in a set environment, where the gut microbiome is the same organism but with their genes attached. [7] The gut microbiota is made up of bacteria, archaea, viruses, fungi, and protozoa. The human gastrointestinal system contains a multitude of diversity in microorganisms. The exact number of microorganisms varies per person and age but is commonly estimated to contain 2776 species with about 22 million bacterial genes and 11 bacterial phyla residing in the human intestinal tract, specifically the gut, where they are most important. [14] More than 90% of the dominant bacterium type are part of the negative Firmicutes and beneficial Bacteroidetes phyla. [2] The human gut microbiota is in a symbiotic relationship with the host and its environment and quickly adapts (within 24 hours) in response to change. [15] Further, the different microorganisms themselves interact in the gastrointestinal tract. The goal of healthy gut microbiota is eubiosis, which refers to a beneficial functional status. [8] During eubiosis the gut microbiota is able to produce short-chain fatty acids such as acetate, propionate, and butyrate which are microbial metabolites from dietary fermented nondigestible carbohydrates. [6] Short-chain fatty acids play a key role in cell differentiation and growth, development of anti-inflammatory agents, modification of the immune system, and regulation of pancreatic beta cell insulin synthesis. [16] In a healthy gut, the immune system can function as an intestinal barrier. However, research has found that different diseases disturb this interaction of the host's immune system and the gut microbiota, possibly harming the intestinal barrier with high inflammation. [14] Gut microbiota also plays an important role in the breakdown and absorption of the amino acid tryptophan, which is involved in the metabolism of serotonin and melatonin which regulates appetite, mood, and sleep. [15] Also, the mucosal Enteroendocrine cells (L-cells) affect appetite regulation through the production of a hormone that affects the gut microbiota composition. [14] The human gut microbiota is also involved in the synthesis of vitamin K and B vitamins, the metabolism of bile acids, and the degradation of dietary polyphenols. [17] Further, the gut microbiota is directly connected through the vagus nerve and the enteric nervous system in multiple body function. [8] This involvement includes the gut-brain axis, the structure of bones, and the cardiovascular system. The gut-brain axis is a term used to describe the biological signaling between the gastrointestinal tract and central nervous system. [1] Consequently, this reveals just how vital the microbiota is for human health. Should eubiosis not be maintained in the gut microbiota, dysbiosis occurs, which may lead to inflammation and leaky gut syndrome. Leaky gut syndrome is not an official medical diagnosis but refers to symptoms of bloating, food sensitivity, and digestive issues, which are said to be due to a disruption of the tight junctions in the gut of the small intestine, allows bacteria and toxins to leak into the bloodstream, causing widespread inflammation. [4] Medically, this may be referred to as endotoxemia, which occurs when Endotoxins are freed through bacterial death and are found in the bloodstream as lipopolysaccharides after crossing the gastrointestinal barrier. [7]

To determine the possible eubiosis or dysbiosis of the gut microbiota researchers collect and analyze fecal samples for consistency using the Bristol stool chart, increase or decrease in microbial diversity, occurrence of short-chain fatty acids, and specific bacteria types such as beneficial Bifidobacterium or undesirable lipopolysaccharides, linked to severe inflammation. Further, inflammation can also be assessed in the fecal sample through decreased alkaline phosphatase (ALP), which are metalloenzymes that catalyze the removal of phosphate groups and are significantly related to the quality of the diet, especially polyunsaturated fatty acids. [18] Studies have shown that taxonomic dysbiosis, a loss of the gut microbiota composition, and metabolic gut dysbiosis are contributors of the development of inflammatory bowel disease, autoimmune disease, colorectal cancer, metabolic diseases such as type 2 diabetes and obesity. [14] In return, these illnesses create a non-beneficial gastrointestinal environment. [14] The gut microbiota of obese individuals is suspected to be less diverse in gut microbiota with a reduced metabolic capacity. [1]

Diabesity

Globally, more people are currently overweight than underweight, showing that obesity has grown into a major health problem. The United States leads the world in prevalence obesity. The 2015 – 2016 NHANES (National Health and Nutrition Examination Survey) reported an obesity incidence rate of 39.8% in adults and 18.5% in children and adolescents. [4] The prevalence of obesity worldwide has nearly tripled since 1975. [19] A person is considered overweight with a BMI of 25 kg/ m^2 or higher and obesity with a BMI of 30 kg/ m^2 or higher. A visual excessive accumulation of adipose tissue can mostly be seen. [10] It seems that obesity is simply caused by an excessive intake of food and beverages and/ or a lack of energy expenditure, but the causes of obesity have proven to be far more complex. [20] These aspects include lifestyle, environment, genetics, and epigenetics with deep-rooted causes found in physiological, psychological, and cultural characteristics. [21] Each person's cause for the development of obesity is differing. Modifiable risk factors for the development of obesity include physical inactivity, quality of sleep, dietary patterns, and excessive food intake. [19] Research has shown, that people with obesity have an abnormal increase in the hormone leptin, which regulates food intake via the hypothalamus. [4] Further, it has been stated that a high fat and hypercaloric diet may lead to a hypothalamic dysfunction which affects leptin production and increases the risk for insulin resistance. [5] Therefore, the cause of obesity can be attributed to western society, with a lack of nutritional education, targeted marketing strategies, and lack of availability and high costs of healthy foods. In non-communicable diseases, such as diabetes, obesity is a significant risk factor as are obesity-related complications. [6]

Type 2 diabetes mellitus accounts for around 95% of diabetes cases diagnosed globally. [22] However, since diabetes is a progressive disease, impaired glucose tolerance may exist long before the diagnosis of type 2 diabetes mellitus. In the early stages of the disease, the individual will most likely not notice the typical symptoms, due to gradual progression. [23] Typical symptoms of type 2 diabetes depend on age and stage but may include glycosuria with the absence of ketones, polydipsia, polyuria, polyphagia, blurry vision, and slower healing of wounds. [12] Most people diagnosed with type 2 diabetes are obese and the higher body weight can contribute to insulin resistance and the destruction of pancreatic beta cells. [12] The characterization of type 2 diabetes mellitus is a combined occurrence of beta-cell failure, increased hepatic glucose production, and insulin resistance. [12] This may be due to deceased tissue sensitivity or decreased responsiveness to insulin in the muscle, liver, or adipose tissue. [12] Even if endogenous insulin production is not affected, the related insulin resistance leads to hyperglycemia. [24] By the time of diagnosis, the body has compensated with insulin hypersecretion, which is followed by a 24% – 65% reduction in beta-cell function. [4] Diabetes mellitus type 2 is diagnosed with fasting glucose greater than or equal to 126 mg/dl, A1C above 6.5%, casual plasma glucose of >200 mg/dl with symptoms, or 2-hour post-load glucose of >200 mg/dl. [12] Studies have shown that type 2 diabetes may have an impact on the bacterial communities which regulate the endocannabinoid system, affecting the glucose and energy metabolism through the gut-brain axis. [12] The endocannabinoid system plays a major role in the development and progression of obesity and type 2 diabetes, and is connected to the growth of specific gut microbes. [25]

Diabesity is the term that refers to type 2 diabetes mellitus associated with obesity. The connection between obesity and type 2 diabetes is due to the extreme accumulation of adipose tissue which contributes to chronic inflammation, insulin resistance, and eventual hyperglycemia. [24] Obesity-related chronic inflammation is suspected to occur in connection to cytokine production in the adipose tissue through the macrophages. [6] These cytokines disturb the tissues relying on insulin, as well as the beta cells, and cause inflammation. [6] Other theories connecting obesity and type 2 diabetes include lipotoxicity, which promotes the damage to peripheral tissues and contributes to the reduced amount of beta cells in the pancreas with overall insulin sensitivity. [22] Further, obesity has been shown to cause insulin resistance, with chronic hyperglycemia leading to the diagnosis of type 2 diabetes mellitus. [12] As for the gut microbiome, diabetes with obesity has been found to affect gut permeability and leading to reduction in the microbiome species that produces short-chain fatty acids and butyrate. [2] Increased production of butyrate has been shown to decrease gut permeability, impact the gut-brain axis and decrease appetite, and improve insulin sensitivity. [2] It has been predicted, that by the year 2025, more than 300 million people will be diagnosed with type 2 diabetes mellitus linked to obesity. [10] However, through targeting obesity, clinicians can achieve beneficial results in improving type 2 diabetes mellitus and its related complications. [12] Targeting weight loss with lifestyle interventions such as diet play a significant role in the clinical management of diabesity.

Mediterranean Diet

Next to medications, stress, chronic disease, choice of diet, and dietary pattern have been recognized as leading aspects that impact the gut microbiota composition in humans. [9] Depending on the type of diet, growth of negative bacterial groups is promoted, resulting in a change in the pH of the intestine, an increase in the gut permeability, and subsequent inflammation. [26] The main macronutrient explored in studies thus far that seems to have shown a large impact on the gut microbiome are carbohydrates. [27] However, micronutrients also contribute to the gut microbiome's health, immune response, and barrier function. [14] Overall, studies have shown that the complete diet composition is more important for the gut microbiome than just certain nutrients, foods or supplements. [14] An overall increase in the consumption of plant-based sources has proved to be especially beneficial. [27] The American "Western-style diet" for instance, is rich in ultra-processed foods, refined sugars, sodium, saturated fatty acids, alcohol, and other harmful components. The minor intake of fruits and vegetables in the Western-style diet led to a reduction in fiber, polyphenols, and micronutrients. [4] This type of diet disturbs the microbiota population, by increasing negative gut bacteria such as Firmicutes, leading to gut dysbiosis with inflammation, following insulin resistance and glucose intolerance. [20]

On the other hand, the Mediterranean diet has shown to have a beneficial impact on the gut microbiome, which is primarily due to prebiotic effects, short-chain fatty acids production, and insulin sensitivity advancement. [14] For the treatment of obesity and type 2 diabetes, among other illnesses, the Mediterranean diet has been demonstrated to be one of the most beneficial diets. [20] The idea of the Mediterranean type diet was first presented in the 1980s by the American physiologist Dr. Ancel Benjamin Keys. [13] The Mediterranean diet is noteworthy for its high amount of polyunsaturated fatty acids, complex carbohydrates, balance of micronutrients, and bioactive compounds. [28] [29] The increased amount of dietary fiber derives mainly from plant sources such as legumes, vegetables, whole grains, and fruits. Further, the polyunsaturated fatty acids have anti-inflammatory properties and are found in the Mediterranean diet in fish, olive oil, nuts, and seeds. [9] Additionally, the bioactive compounds have antioxidative properties found mainly in flavonoids, phytosterols, and polyphenols. [28] The Mediterranean diet increases the growth of beneficial Bacteroidetes and other bacterial groups which leads to eubiosis. [8] The Mediterranean diet for primary prevention of cardiovascular diseases: Prevención-con-Dieta-Mediterránea (PREDIMED) study showed that the Firmicutes to Bacteroidetes microbiota ratio in the host feces plays a major factor in the production of short-chain fatty acids and overall health. [14]

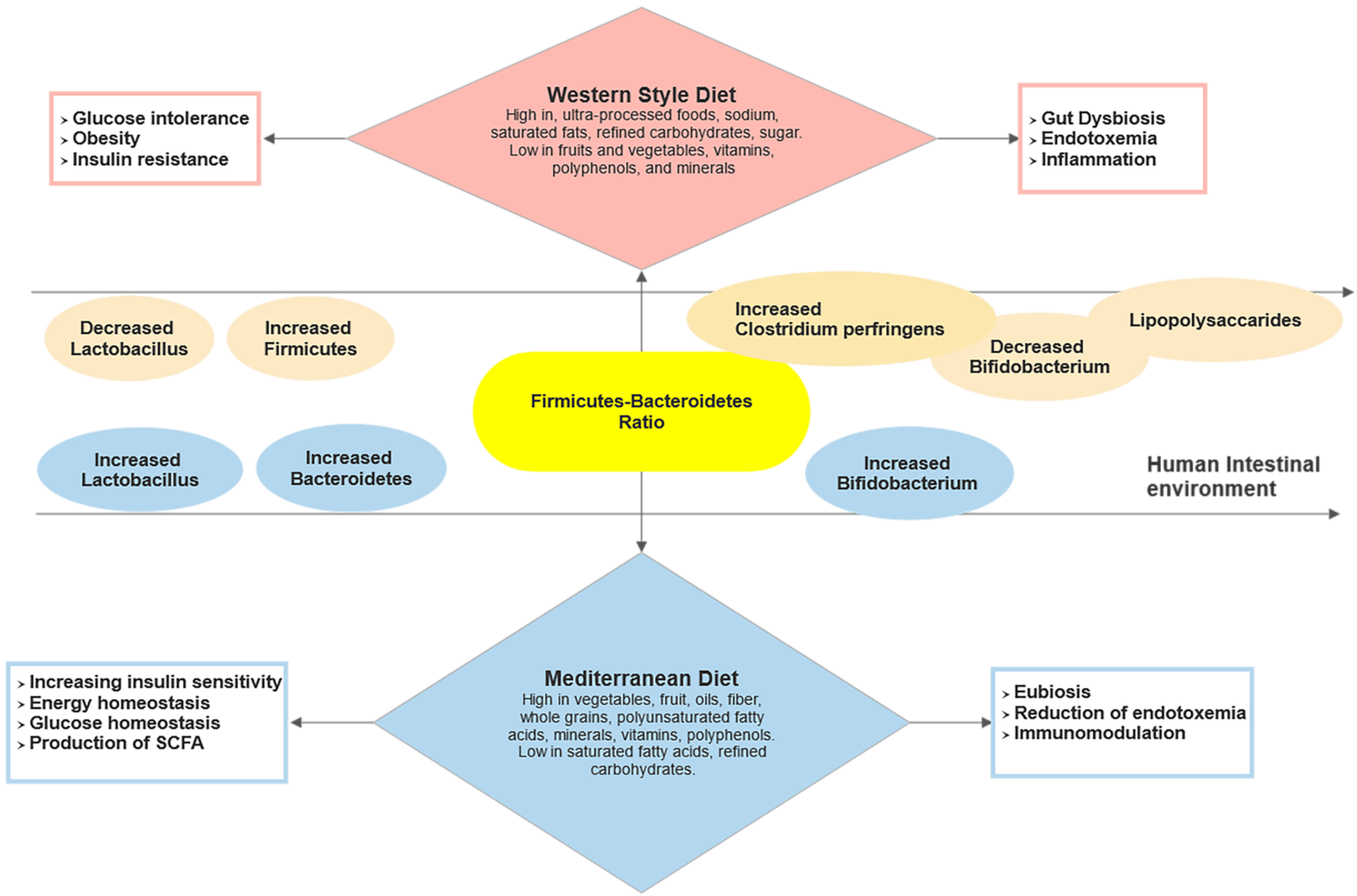

Figure 1. Dietary effects on gut microbiota.

Since the Mediterranean diet is very low in saturated fatty acids but high in mono- and polyunsaturated fatty acids, it promotes the growth of beneficial gut bacteria. [8] Olive oil particularly has approximately 70% to 85% monounsaturated fatty acids, with a high content of oleic acid. [14] The consumption of olive oil seems to increases the growth of Bifidobacterium and Lactobacillus due to the high amount of monounsaturated fatty acids. [8] These 2 beneficial lactic acid bacteria affect the gut microbiome by increasing butyrate production with their inflammatory ability. [14] The essential polyunsaturated fatty acid omega 3 is highly anti-inflammatory and plays a major role in cell membranes. [17] The polyunsaturated fatty acid omega 3 in the Mediterranean diet is mainly due to the high consumption of fresh fish, seafood, nuts, seeds, and oils. The Mediterranean diet supports the appropriate 2:1 (Omega 6: Omega 3) ratio for omega 6 not to have a pro-inflammatory effect. [4] In fecal testing, high qualities of omega 3 in the Mediterranean diet have shown increases the beneficial Bacteroidetes and reduces in negative Firmicutes gut bacteria leads to reduces inflammation. [8] The gut microbiome also seems to have the ability to metabolize polyunsaturated fatty acids from the diet which may decrease the risk of inflammation and obesity through the production of microbial metabolites. [14]

Complex carbohydrates, also referred to as dietary fiber, are non-digestible in the small intestine but fermentable by our gut microbiota. [23] This fermentation process through the gut bacteria has a probiotic effect, resulting in the production of short-chain fatty acids and butyrate which promotes beneficial Bifidobacterium and Lactobacilli. [14] The Mediterranean diet is rich in complex carbohydrates through whole grains, vegetables, and fruits which have been found to reduce the risk of developing type 2 diabetes and other diseases. [21] Soluble fiber is predominantly fermented by the gut microbiota in the distal intestine and produces short-chain fatty acids. [28] [1] The beneficial effect of soluble fiber is due to the short-chain fatty acids which are a source of energy for the colonocytes, increase intestinal mucosa growth, and increase satiety with subsequent body weight control. [1] Oat and barley are a great food source which provide the polysaccharide Beta Glucan. [28] Insoluble fibers are beneficial as well by restricting energy intake leading to increased colonic fermentation and insulin stability. [27] Cellulose is an insoluble fiber found in vegetables and fruits such as green beans and bananas, which increases microbiota variety and, gut transition, and reduces fermentation time in the colon. [20]

Another important component of the Mediterranean diet is polyphenols. Polyphenolic compounds, including flavonoids, are commonly found in almost all types of dietary plants and are metabolites that are anti-inflammatory antioxidants. [3] Polyphenols are valuable for the gut microbiome due to the increase in beneficial Bifidobacterium and Lactobacillus, through a prebiotic and anti-inflammatory effect. [14] Polyphenols in the Mediterranean diet are mainly found in fruits such as berries, grapes, and apples but also in soy, coca, tea, olive, and nuts. [3] Aromatic plants and spices such as basil, oregano, rosemary, and thyme are also high in polyphenols, widely used in the Mediterranean diet. [30] Further, polyphenols in the gut microbiota are involved in tryptophan metabolism, which takes part in the regulation of serotonin and melatonin that control appetite, mood, and sleep. [8] [15]

Additionally, the Mediterranean diet is high in vitamin composition and diversity. Studies have shown these essential compounds to be vital to the microbiome's effectiveness and its immune function. [14] The fat-soluble vitamins D and A are crucial for the modulation of the gut microbiome, establishing a stronger barrier function through tighter junctions, beneficial composition, and creating homeostasis in the intestine. [8] A deficit in vitamin D and vitamin A can lead to a severe decrease in beneficial Bacteroidetes, which increases inflammation, dysbiosis, endotoxemia, and insulin resistance for obesity and type 2 diabetes mellitus. [14] Vitamin A can be found in the Mediterranean diet in foods such as beef liver, different cheeses, carrots, peppers, spinach as provitamin A. [1] Vitamin D, specifically cholecalciferol, is abundant in foods consumed in the Mediterranean diet such as salmon, tuna, mackerel, cheese, and egg. [1] The other fat-soluble vitamin of interest may be vitamin E due to its ability to shield the gut mucosa from reactive oxygen species. [14] Food sources of vitamin E in the Mediterranean diet are vegetable oils, nuts, and seeds. [4] However, further research may be necessary to determine vitamin E's effectiveness on the gut microbiota. Most research conducted thus far has only been in mice models which showed an increase in Firmicutes and decrease in Bacteroidetes altered the composition of the gut microbiota and lead to obesity and type 2 diabetes. [14] Studies of the water-soluble vitamin C have shown benefit to the gut microbiome due to increased destruction of negative microbiomes. [14] Food sources of vitamin C in the Mediterranean diet are fruits and vegetables such as citrus fruits, tomatoes, red pepper, and brussels sprouts. [1] Humans cannot synthesize the water-soluble B vitamin complex, however, it is essential for overall health, as it is involved in many enzyme cofactors. [17] The vitamin B complex includes Thiamine (B1), Niacin (B3), Pantothenic acid (B5), Pyridoxine (B6), Biotin (B7/B8), Folate (B9), and Cobalamin (B12). [17] These vitamins have to be consumed through the diet but can also be produced by specific bacteria in the gut microbiota, thus proving how the host and gut microbiome entwine. [8] Foods sources of vitamin B in the Mediterranean diet are milk, cheese, eggs, meat, tuna, and salmon. [17] A deficiency in the B vitamin complex can lead to inflammation associated with type2 diabetes mellitus, dysbiosis, decreased junction tightness, and an increase in Firmicutes, and a decrease in Bacteroidetes. [14]

The final component that can be found in higher amounts in the Mediterranean diet is minerals. Minerals that seem to impact the gut microbiota include Zinc, Iron, and Selenium. [8] These minerals affect the gut microbiome positively through their immunomodulation ability, reduction in intestinal inflammation, growth of beneficial commensal bacteria in the intestine, and increased microbial diversity. [14] Foods sources of Zinc, Iron, and Selenium in the Mediterranean diet are oysters, crab, lobster, beef, pork, chicken, and legumes. [17] Alternatively, unabsorbed iron in the intestinal lumen can increase the growth of pathogenic bacteria in the colon. [14] An increase in beneficial Bifidobacterium through diet can counteract the possible damage caused by free iron radicals by binding them in the large intestine. [14] However, further research is required to determine the specific connections between the gut microbiome and the impact of each specific mineral.

Overall, the Mediterranean diet has a high number of nutritional elements which appear to positively impact the gut microbiome and the chronic disease diabesity. The Mediterranean diet seems to affect beneficial bacterial growth, leading to a healthy gut microbiome and immune system function.

Table 1.

The role of Mediterranean diet components on the gut microbiota.

Nutrient	Food Source	Recommended Intakes	Gut Microbiome Effect
Monounsaturated fatty acids	Olives and Olive oil	NA	↑ Bifidobacterium ↑ Lactobacillus ↑ Butyrate production
Polyunsaturated fatty acids	Vegetable oils, fish, nuts, and seeds	NA	↓ Anti-inflammatory ↓ Lipopolysaccharide
Omega 3 fatty acids	Fish, seafood, nuts, seeds, plant oils, eggs	1.6 g (male) 1.1 g (female)	↑ Bacteroidetes ↓ Firmicutes ↓ Lipopolysaccharide
Polyphenols and flavonoids	Berries, olives, nuts, spices, herbs, seeds	NA	↑ Lactobacillus ↑ Microbial diversity ↓ Dysbiosis
Dietary fiber (Soluble and insoluble)	Fruits, vegetables, whole grains	25–30 g per day	↓ Inflammation ↑ SCFA production ↑ Microbial diversity ↑ Bifidobacterium ↑ Lactobacilli ↑ Colonic fermentation

Nutrient	Food Source	Recommended Intakes	Gut Microbiome Effect
Vitamin A	Beef liver, cheese, carrots, peppers, spinach	900 µg	Maintain diversity ↓ Firmicutes ↑ Tight junctions
Vitamin D	Salmon, tuna, mackerel, cheese, and egg yolk	15 µg	↓ Firmicutes ↑ Tight junctions
Vitamin C	Citrus fruits, tomatoes, red pepper, and brussels sprouts	90 mg (male) 75 mg (female)	↑ Destruction of pathogens Antioxidant
Vitamin B complex	Cheese, eggs, liver, whole grains, beef, poultry, pork, tuna, salmon	Differs for each vitamin	↓ Dysbiosis Anti-inflammatory Fuel for Bifidobacterium and Lactobacillus
Zinc	Oysters, beef, crab, lobster, pork, chicken, legumes	11 mg (male) 8 mg (female)	Anti-inflammatory
Selenium	Seafood and meat	55 µg	↑ Microbial diversity

These recommended intakes are for normal adults and may change in the elderly, pregnancy and lactation, or children. The recommendation may also change in disease stages or chronic status. For some nutritional compounds are recommendations for specific dosages.

Methodology

A systematic literature search was performed in May and June 2021, using Kansas State University Libraries, PubMed, and Medline database to identify relevant articles with publication dates from 2011 through June 2021. All data considered for inclusion originated from peer-reviewed published articles of prospective epidemiologic revisions, human studies, and were written in English. For data and statistics, the search strategy implemented was similar for the World Health Organization (WHO) and Center for Disease Control (CDC). Textbooks and other references were also included for background clarification and assessment of evidence. The medical subject headings and text words covered a broad range of factors on the gut microbiome, Mediterranean diet, obesity, and type 2 diabetes components. Definite keywords, searched as text words in the title, abstract, and full journal article were used in a search string for a variety of terms and included a combination of the following aspects. Microbiome terms used included "microbiota", "intestinal mucosa and microbiology", "gastrointestinal tract and microbiology", "gastrointestinal and diseases and microbiology". The dietary search component included probing on a broad category of diet, which was then focused on Mediterranean components and included "Mediterranean diet", "food", "polysaccharides", "complex carbohydrates", "nutrition", "vitamins", "fatty acids", "dietary fiber", "prebiotics", "probiotics", "polyphenols", "minerals", "diet, western", and "whole grains". The disease search for type 2 diabetes and obesity elements included "type 2 diabetes mellitus", insulin resistance, "impaired glucose homeostasis", "obesity", "overweight", "BMI of 30 kg/m2", "excessive food intake", and "adipose tissue". In addition, the bibliographies of the WHO, CDC, and American Diabetes Association reports on diabetes and obesity, review articles, and meta-analyses pertaining to the gut microbiome and diabesity were examined to identify all available literature that may not have been identified by the database searches. The choice of this analysis was microbiome, Mediterranean diet, and diabesity. Manual searches through reference lists of the articles were also performed to identify additional studies.

Articles that did not report the consequence or prevention of a dietary intervention specific to the Mediterranean diet or its components on microbial composition and type 2 diabetes and obesity were excluded. It was challenging to limit the studies to only the Mediterranean diet and gut microbiome considering diabesity since most studies included other diet patterns and/ or disease stages as well. Further, it was challenging to limit evidence to the Mediterranean diet and vegetarian diet (e.g., whole grains, low saturated fats, low sodium, low refined sugars), as they are generally correlated with healthy dietary patterns, whereas the Western-style diet (e.g., high refined sugar intake, high sodium, smoking, alcohol, refined grains, low fruit, and vegetable intake) generally has a negative association. Studies that assessed nonpharmacological and surgical interventions were included.

This search resulted in a total of 153 articles being selected for broader evaluation and inclusion in this review. The final review included 12 studies that describe the relationship between specific dietary components and intestinal microbiota composition and/or type 2 diabetes and obesity. Study designs primarily included randomized controlled trials, cross-sectional studies, case-control studies, in vitro studies, and reviews. Additionally, to establish the dietary impact on the microbiome under measured trial circumstances, animal studies, reviews, and research were also included.

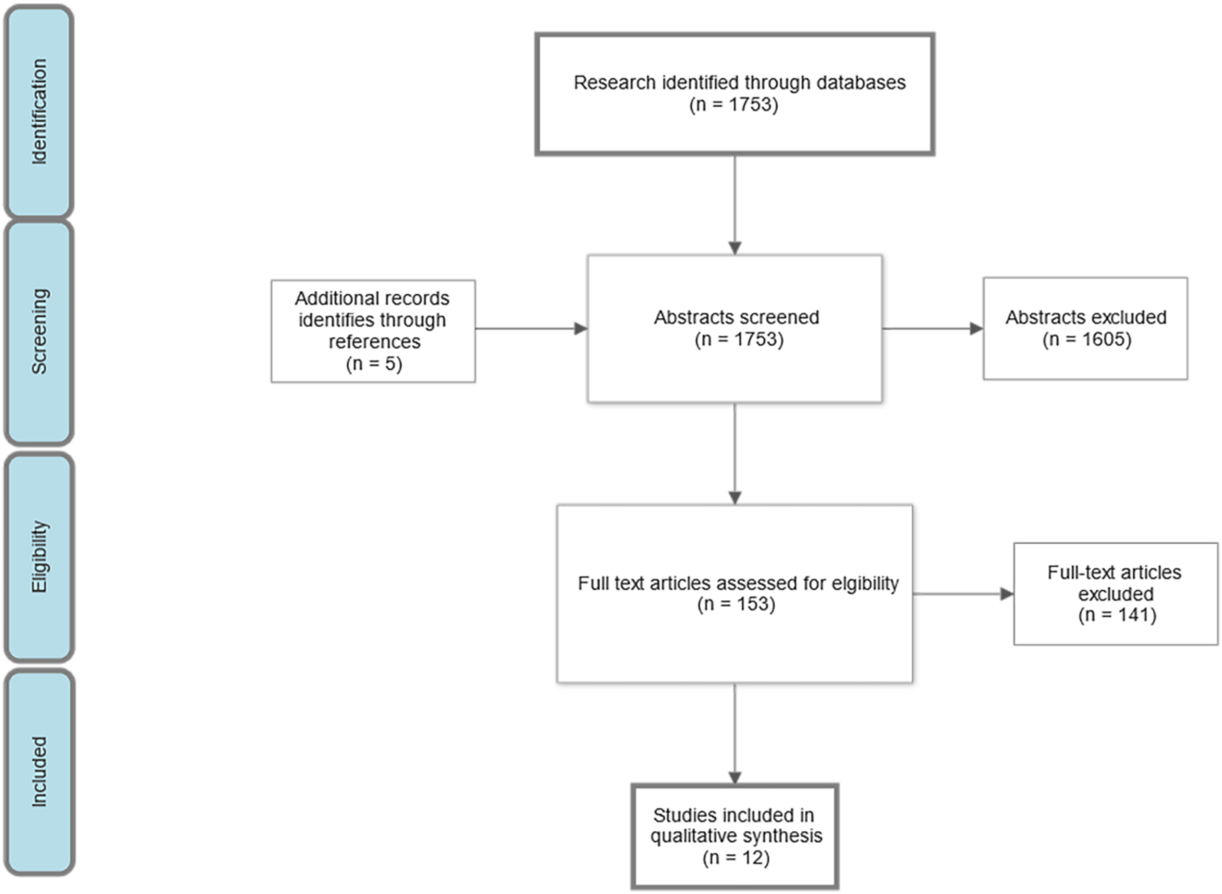

Figure 2. A flowchart of the methodology used for the report.

Results

The results of my findings are as follows. A systematic review of 8 meta-analyses and 5 randomized controlled trials, by Katherine Esposito et al., assessed the effectiveness of the Mediterranean diet on obesity and type 2 diabetes management. [26] The study evaluated disease progression in adults at risk for or with type 2 diabetes. The consumption of a Mediterranean diet led to a risk reduction for the development of type 2 diabetes mellitus of 19% to 23%. [26] Further, the Mediterranean diet resulted in reduction of glycated hemoglobin (HbA1c) from 0.30% to 0.47%, and a decrease of fasting plasma glucose of 13 mg/dL compared with other controlled diets. [26] A beneficial effect on cardiovascular risk factors was also demonstrated. The study concluded that the Mediterranean diet improved glycemic control compared to other eating patterns, for the development and management of type 2 diabetes but that further cause and effect needs to be investigated. [26]

A pilot study by Shámila Ismael et al. assessed the effect of the Mediterranean diet on adult patients with type 2 diabetes not on insulin but oral glucose-lowering medication and their gut microbiome. [18] The study duration was 12 weeks. The study included 9 patients that received baseline Mediterranean diet counseling and underwent fecal sampling, body composition, and biochemical markers. [18] Study follow-up included 24-hour dietary recalls, 2-week intervals nutrition counseling, fecal testing with the use of the Bristol stool scale for consistency, as well as bacterial diversity, and biochemical markers. After 12 weeks, results showed an average decrease in BMI from 27 to 26, a reduction in HbA1c of 0.67%, a decrease in fasting glucose levels from 131 to 120 mg/dl, a decrease in inflammatory markers, and an increase in bacterial diversity with a reduction in Firmicutes and increase in Bacteroidetes. [18] The authors concluded that the Mediterranean diet resulted in an improved glycemic control in type 2 diabetes, and postulated that gut microbiome homeostasis plays a probable role in the metabolic effect even with the study's small sample size. [18]

The literature review by Miguel A. Ortega et al. investigated the possible role of obesity and type 2 diabetes mellitus in the development of diabesity and its connection to the gut microbiome. [6] The study found that obesity and type 2 diabetes seem to change the gut microbiome composition, resulting in reduced Bacteroidetes and butyrate production, increased appetite, reduced insulin sensitivity, and energy metabolism. [6] Further, the Mediterranean diet seems to benefit diabesity reducing dysbiosis and endotoxemia which then regulates the gut microbiome population and increases the growth of beneficial gut bacteria. [6] The authors concluded that the Mediterranean diet substantially improves the gut microbiota, which in turn improves the clinical management of diabesity. Even though more studies are needed to establish cause and effect, the disruption of the microbiome and dysbiosis may be involved in the development of obesity and diabetes. [6]

The review from Cani P.D. et al. explored the link between the endocannabinoid system and the gut microbiome, inflammation, obesity, and diabetes. The findings showed that the endocannabinoid system is affected by a specific microbiome in the gut which increases or decreases the activity and its effect on energy metabolism. [25] Further, they found a clear difference in the gut microbiome composition between lean versus obese and obese people and individuals with obesity and type 2 diabetes. [25] They concluded that there is a clear connection between dietary interventions and the ability of specific gut microbes to control host functions that regulate energy homeostasis, glucose metabolism, and inflammation in people with obesity and type 2 diabetes mellitus. [25]

The review by Cielo García-Montero et al. assessed the difference in gut microbiome with the consumption of a Mediterranean diet versus a Western-style diet in connection to inflammation and non-communicable diseases. [14] It was found that the Mediterranean diet is a well-balanced diet that is high in components that beneficially affect the intestinal epithelial barrier, and commensal bacteria growth, which is anti-inflammatory and decreases the burden on non-communicable disease. [14] They concluded that micronutrient deficiency in malnutrition of obesity and type 2 diabetes contributes to a lack of short-chain fatty acids and increased inflammation. [14]

The clinical trial conducted by Maria Luisa Eliana Luisi et al., assessed the connection between the Mediterranean diet, with a special focus on olive oil, and gut microbiome in obesity and type 2 diabetes. [30] The study included 18 Italian adults with a BMI above 25 kg/ m^2 and 18 adults with a BMI of 18.5–24.9 kg/ m^2 who were given a Mediterranean diet containing 40g of olive oil per day for 3 months. Feces and blood samples were collected at baseline and after 3 months. A reduction in body weight and BMI was reported in both groups. [30] Further, olive oil, which is high in polyphenols, contributed to the growth of beneficial Lactobacillus bacterium, which supports the preservation of the gut microbiome, reduced inflammatory markers, and increased host immunity. [30] The study concluded that even though the Mediterranean dietary pattern has a beneficial effect on the increase in specific bacterium, the relationship connecting dietary behaviors and the microbiome is still not fully understood. [30]

Zengliang Jiang et al, assessed 1879 Chinese adults with a food frequency questionnaire and fecal metabolite test beginning from 2008 through 2019, for a possible association between increased fruit and vegetable intake and the gut microbiota and their related metabolites and type 2 diabetes mellitus. [31] The results showed a connection between increased dietary fruit intake and an increase in the beneficial gut microbiome, protective effect, as well as gut microbiota diversity, and composition. [31] The highest microbial biomarker of fruit intake at mean was 149 g/day (3/4 cups), found in banana, apple, and grape which showed to reduce type 2 diabetes risk by 17%. [31] The study concluded that the human gut microbiome is vital in the prevention of type 2 diabetes and that reduced risk arises through the protective effect of increased dietary fruit intake on the restructured gut microbiome and metabolic alteration. [31] It was acknowledged that the lack of impact of vegetables may be due to the cultural dietary pattern of cooked vegetables. However, it has been shown that a healthy diet pattern, including increased fruits and vegetables, beneficially influences the gut microbiome and may reduce the risk of type 2 diabetes mellitus and obesity.

The Spanish review article by Patricia Lopez-Legarrea et al. assessed the impact of different dietary patterns and aspects on the gut microbiome on obesity and inflammation. [28] The research showed that beneficial Bifidobacterium are reduced and negative Firmicutes are increased in obese individuals with increased inflammation. [28] However, a dietary intervention of Mediterranean nutritional regime high in polyphenols and polyunsaturated fatty acids increased beneficial Bifidobacterium and Lactobacillus, with a decrease in inflammation measured in C-reactive protein. [28] Also, the intake of red wine showed a decrease in the negative Clostridium perfringens pathogen which is highly connected to obesity and type 2 diabetes. [28] The article concluded that the Mediterranean diet approach proved to be the most beneficial to offset obesity and type 2 diabetes mellitus by maintaining an advantageous gut microbiota structure. [28] However, more research is required to determine the impact of each micro-and macronutrient on the gut microbiome.

The review by Louise Brunkwall et al. assessed the connection of the gut microbiome as treatment and prevention for type 2 diabetes mellitus. The study found that fecal consistency and dietary pattern contribute to the diversity and composition in gut microbiota, an increase in beneficial Lactobacillus species amongst people with type 2 diabetes may result from the treatment with metformin, and specific gut bacteria are decreased in the onset time of type 2 diabetes. [32] The research concluded that there is a connection between type 2 diabetes and low dietary fiber intake, which may lead to a decrease in gut microbiome producing short-chain fatty acids affecting energy homeostasis. [32] Further, they concluded that metformin's glucose-lowering effects are controlled by the makeup of the gut microbiome; therefore, altering the gut microbiome may be used as a potential therapy to improve the glycemic levels in people with type 2 diabetes. [32]

The systematic review by Rasnik K. Singh et al. assessed the impact specific dietary components have on the gut microbiome and chronic disease including obesity and diabetes. The research found that intake of certain foods creates a change in host gut bacteria, and negative Firmicutes bacteria are increased in obesity. [20] Further, a low non-digestible carbohydrate, low plant protein, and low fermented foods comprised of lactic acid bacteria diet showed a decrease in bacterial abundance and beneficial Bifidobacterium as well as Lactobacilli, and a decrease in short-chain fatty acids with a reduction in the amount of butyrate in the feces of patients and increased inflammation, obesity, and type 2 diabetes. [20] The study concluded that diet can alter the microbiome in the gut, which affects host immunity, insulin sensitivity, metabolic parameters, and overall health. [20]

The Italian systematic review by G. Blandino et al. assessed the impact of the gut microbiome on diabetes. The review discovered that an increase in beneficial Lactobacillus bacterium in type 2 diabetes mellitus patients was positively associated with decreased HbA1c and fasting glucose levels. [33] The gut microbiome of type 2 diabetes patients lacks butyrate-producing bacteria. The oral glucose medication metformin has shown an increase in beneficial Akkermansia muciniphila bacterium which seems to be connected to body weight, glucose, and inflammation regulation. [33] Further, an increase in Bacteroidetes and decrease of Firmicutes has shown to decrease plasma glucose levels in type 2 diabetes mellitus patients. [33] The research concluded that the gut microbiome plays a vital part in the regulation of obesity, type 2 diabetes mellitus, and inflammation development and control which can be impacted with dietary interventions such as polysaccharides. [33]

The Italian systematic review by Giuseppe Merra et al. assessed the connection between the gut microbiome and the Mediterranean diet in the prevention of chronic non-communicable diseases. [13] The review showed a beneficial impact of the Mediterranean diet on the profile and biodiversity of the gut microbiome, increasing Bifidobacterium and short-chain fatty acids in the intestine. [13] The gut microbiome is strongly influenced by pre-and probiotics and extra virgin olive oil of the Mediterranean diet, decreasing body weight, inflammation, improve glucose metabolism, and increases intestinal barrier function. [13] The article concluded that the Mediterranean diet affects the gut microbiome through an increase in diversity, which increases beneficial gut bacteria and reduces the risk for development and treatment of chronic non-communicable diseases such as obesity and type 2 diabetes mellitus. [13]

Discussion

In history, the Mediterranean diet is one of the most frequently recommended dietary interventions for the prevention and treatment of chronic diseases such as hypertension, hyperlipidemia, obesity, and type 2 diabetes mellitus. The Mediterranean diet is recognized to have a beneficial impact the gut microbiome due to the balance it provides between whole grains, fatty fish, olive oil, herbs, nuts, seeds, wine, and fresh fruits and vegetables. Further, carbohydrates in the Mediterranean diet are usually below 50% of the daily energy intake which has shown to reduce diabetes rates and improve glycemic control of type 2 diabetes mellitus. [13] The human gut microbiome plays a major role in energy and nutrient metabolism, metabolite production, immune system modulation, and gut barrier integrity. [32] Recent studies have shown that people with type 2 diabetes have increased inflammatory processes with a changed gut microbiome homeostasis that decreases bacterial diversity, increases negative Firmicutes bacteria, and reduces beneficial Bacteroidetes bacteria. [33] However, the specific connection to how the Mediterranean diet in obese and type2 diabetes mellitus individuals impacts the gut microbiome and vice versa is not entirely clear.

Research revealed that the Mediterranean diet has been one of the most fascinating approaches in the management of the composition of the microbiome in people with type 2 diabetes and obesity, especially in the European regions. It is said that the success of the Mediterranean diet is due to its high prebiotic compounds which can correct gut dysbiosis existing in diabesity. [6] Further, the Mediterranean diet in obesity and type 2 diabetes may result in homeostasis of the gut microbiota, through reduction of bacterial translocation and lipopolysaccharides, and is associated with an improved barrier function of the intestine, due to increased production of short-chain fatty acids that stimulate the excretion of glucagon-like peptide 1 (GLP-1). [18] [25] The peptide GLP-1, secreted from intestinal L-cells is beneficial for diabesity due to the increase in insulin secretion and growth of β-cells, the impairing impact on glucagon, the gastric voidance, and followed food intake. [22]

Also, specific gut microbiomes affect the endocannabinoid system through the gut-brain axis. [12] All of these aspects contribute to a variety of beneficial effects on diabesity such as increased energy expenditure, decreased food intake, inhibited fat buildup, improved glucose metabolism, improved insulin sensitivity, reduced intestinal permeability, reduced inflammation, and improved insulin secretion through pancreatic β-cells. [21] [18] The impact of the Mediterranean diet on the gut microbiome can help control body weight, resulting in a reduction in fasting blood glucose and HbA1c in individuals with diabesity, which is associated with a decrease in microvascular complications. [18] Thus, the Mediterranean diet has a seemingly direct influence on the gut microbiome in regards to obesity and type 2 diabetes and its prevention and treatment. [16]

It seems that the gut microbiome, particularly bacterial diversity, plays an important role in the treatment of diabesity. The main bacterial group that appears to impact blood glucose and weight control in diabesity is the Firmicutes to Bacteroidetes ratio. [5] The Mediterranean diet, with its non-digestible dietary fibers, offers a valid therapy through probiotic effect on the gut microbiome in diabesity through an increase in positive Bacteroidetes resulting in anti-inflammatory markers. [14] Also, the use of Kefir in the Mediterranean diet may be beneficial on specific gut microbiome as it showed reduction in HbA1c and fasting blood glucose in diabesity. [34] Another noteworthy aspect of the Mediterranean diet in the development and possible treatment of diabesity may be the protein enzyme ALP, which has shown to be reduced in individuals with type 2 diabetes, leading to a change in the gut microbiome with increased lipopolysaccharides, increasing inflammation, increasing gut permeability, and decreasing insulin sensitivity. [18] The consumption of a Mediterranean diet can increase ALP through Zinc-rich foods such as oysters, yogurt, fruit, and nuts. [8] These findings show that more registered dietitians need to get engaged through healthcare and provide effective support, focusing more on dietary intervention in diabesity in connection to the gut microbiome, increasing the overall quality of life.

Another possible treatment option for obesity and types 2 diabetes may be the “Phage therapy” which introduces specific beneficial gut bacteria into the gut microbiome. [6] However, the results of the use of different probiotic strain supplements did not show promising effects since it did not improve overall HbA1c in diabesity. [2] Further, the pharmaceutical treatment seems to impact the gut microbiome and its beneficial bacteria as well, but further research is required. Metformin may increase the production of short-chain fatty acids, reduces intestinal permeability and endotoxemia, and stimulates the activity of endocrine cells through an increase in GLP-1. [2] Also, as depression is often connected to the development in individuals with diabesity, the gut microbiome may also be used to treat mood disorders and depression. [20] Similarly, the development of type 1 diabetes and latent autoimmune diabetes in adults (LADA) has been proposed to be connected to the gastrointestinal microbiome and diet, with inflammation having an activating consequence on diabetes autoimmune disease. [33]

Limitations

Possible limitations of my findings, even though they are valuable, maybe due to differing methods of dietary intake assessments. Some of the differing dietary assessments included assessment at a single timepoint, and self-reported intake, based on a food frequency questionnaire which may interfere with correctness due to recall and measurement errors or bias. To reduce this bias, some of the studies included a dietitian who educated the individuals on food quantities and food labels, asking the participants to take photos of the foods consumed. Also, adherence of individuals to the Mediterranean diet was essential to successful weight loss and glycemic control in individuals with diabetes and obesity. Further, there was inconsistency in the definition of the Mediterranean diet, especially since the main source of dietary fat was not always olive oil. However, even with the difference in definition, consumption of a Mediterranean style diet consistently resulted in HbA1c reduction compared to other dietary patterns. [18]

Some of the research results included in this review may be affected by geographical and cultural limitations such as availability and consumption of certain foods. For instance, in the Chinese culture vegetables are mainly consumed cooked whereas in the Mediterranean diet vegetables are mainly consumed fresh which could potentially result in different gut microbiome and outcome for the treatment of diabesity. [14] Further, residing in an environment that has good resources for healthful foods and physical activity showed a reduction in type 2 diabetes and obesity frequency of 38%, versus an environment lacking in healthy lifestyle encouragement. [21] More data collection is required on the Mediterranean diet and the gut microbiome in diabesity in other cultures and whether adherence to this specific eating pattern is feasible as dairy products, cooking techniques, and oils may differ greatly.

Further, the gut microbiome varies greatly depending on the age of the individuals and their ability to metabolize nutrients which could influence outcomes. For instance, a species of probiotics that are beneficial for a younger age group may be harmful to older adults. [34] Therefore, targeting the gut microbiome as a nutritional intervention for diabesity management and control requires an individual approach, to achieve beneficial effects, as one size does not fit all. Further, standardized procedures to identify and analyze the gut microbiome and inflammation need to be established. Sequencing techniques to give appropriate assessments are very helpful but cost can be prohibitive for microbiota profiling. [6] Also, consider the large spectrum and diversity of bacterial strains, it is challenging to identify specific beneficial or negative strains for an entire population.

When research is conducted, it is important to establish specific selection criteria to reduce errors and strengthen evidence. For instance, the diagnosis criteria of type 2 diabetes in accordance to the American Diabetes Association criteria, time since diagnosis, exclusion of other types of diabetes such as mature diabetes of the young (MODY), identical type of antidiabetic drugs and treatment, explicit HbA1c levels at baseline, and supplements and other medications taken should be considered for study inclusion as these aspects can influence the gut microbiome in diabesity and outcomes in nutritional intervention with the Mediterranean diet. [24]

A large number of mouse models can be found on the connection between gut microbiome and diabesity, and it was challenging to separate the human evidence on this topic. Further, trials of longer duration with a greater number of participants are required to show how the Mediterranean diet affects the gut microbiome in the control of obesity and type 2 diabetes mellitus. A broader evaluation of diversity in foods and food components, as well as bacterial strains, would be required to make accurate and detailed nutritional recommendations to clients.

Conclusion

The World Health Organization anticipates that by 2030 type 2 diabetes in connection with obesity will be the seventh most cause of mortality. [19] This demonstrates that there is an imperative need to develop more efficient treatment and especially prevention approaches. As acknowledged by Hippocrates, “all disease begins in the gut”. [33] The human gut microbiome with its range of involvement in the health of the host is an exceptional, diverse, lively, and essential component of the physiological function of our body. Many aspects shape the composition and capacity of the gut microbiome but the main factor remains nutrition. Changes in the diet can alter the gut microbiome and shift rapidly. Following this, the gut microbiome has become a fascinating tool to assess the effectiveness of the nutritional intervention in the metabolic control of people with obesity and type 2 diabetes. Even though an increase in specific dietary components may be helpful, a complete adaptation of a beneficial diet pattern has shown to be more important for the gut microbiome’s overall health. People with diabesity who adapted to a Mediterranean diet pattern were found to have lower fasting glucose, HbA1c, weight loss, and reduced cardiovascular risk factors. This compared to the Western-style diet suggests that the effectiveness of the Mediterranean diet on type 2 diabetes and obesity is due to the modulation of the gut microbiome. With this knowledge, if a higher intake of fruits, vegetables, whole grains, oils, and nuts were promoted through campaigns in the general population, it could have a significant effect on the increasing challenges and complications diabesity brings. Overall, while further research is required to completely comprehend the physiological processes associated with the development and progression of diabesity, the gut microbiome seems to be a promising focus in the prevention and treatment of diabesity.

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