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Chapter

Mitigating Diabetic Foot Ulcers: The Effect of Diet and Microbiome

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Abstract

To truly eliminate the possibility of diabetic foot ulcers, the elimination of the symptoms of diabetes is essential. There are many forms of diabetes and there is no one diet that is effective for all patients. It is essential that a proper diet is utilized and for most diabetic patients a reduction in weight and the restoration of a properly balanced microbiota can eliminate the devastating effects of diabetes including foot ulcers. This review examines in detail the different types of diets, and how they affect the host and the microbiota to eliminate as much as possible the risk of foot ulcers. Microbiota, diet, incretins, and insulin all directly affect the deposition of fats which causes insulin insensitivity and diabetes in most patients.

Keywords: incretin, SCFA, diabetes, carbohydrates, fats

1. Introduction

Type 2 Diabetes Mellitus (TTDM), which is approximately 95% of all diabetic patients in 2010, affected 280 million (approximately 6.2%) of the world’s population and is thought to increase to 75% by 2030 [1, 2]. This is thought to be due to an increase in the number of obese individuals which leads primarily to an increase in their incidence of TTDM. Most scientists and medical professionals believe that obesity begins at a BMI of 30 and severe obesity at a BMI of 40 but many studies are now suggesting that BMI is not a truly accurate measure of obesity [3]. Most TTDM patients are obese and about 2-3 percent of patients have current active foot ulcers and up to 25% will eventually develop foot ulcers [4]. This occurs as a result of uncontrolled diabetes that interferes with wound healing, reduces pain response, and causes problems with proper blood circulation. Although ulcers can actually occur anywhere on the body, the feet are most vulnerable.

The chief cause of foot ulcerations is due to diabetic neuropathy. High blood glucose levels cause arteries to harden and develop plaques that limit blood flow to tissues including nerves and the heart. This causes reduced nutrient and oxygen uptake by the nerves causing neuropathy. Diabetic neuropathy affects both the somatic as well as autonomic nervous systems resulting in a complex group of pathophysiological disorders. One of the manifestations of these disorders in the diabetic foot which can result in anatomical and physiological changes in the foot such as ulcerations and infections because of a lack of wound healing and a delayed immune response. Since
the feet are frequently covered and the soles are exposed to compression from walking feet when it comes to ulcerations, the feet are the most vulnerable part of the body. Wound healing is slowed for several reasons. Hyperglycemia is a contributing factor to atherosclerosis. This limits the blood flow, especially to the heart but also to any wounds and the feet tend to be even more susceptible [5, 6]. Nerve damage can cause a loss of sensation in the foot and peripheral vascular disease that can go unnoticed. If these conditions become severe enough, this can cause further damage to bone, joints, and soft tissue and if not treated can eventually lead to amputation [7, 8]. Life expectancy following amputation is about 50% within five years [9, 10] although many of those deaths could be due to contributing comorbidities related to diabetes-induced cardiovascular disease [3].

It would seem to suggest that control of diabetes and its symptoms would be the best way to prevent ulcerations. However, it does not fully eliminate the risk [11]. There are two major forms - Type 1 and Type 2 diabetes but there are other less well-known forms as well which include gestational and atypical diabetes. They have very similar symptoms, but their causes can be quite different and are often misdiagnosed [12]. If the weight and diet are left unchanged despite control of diabetic symptoms, there is still a risk of ulcerations, especially on the feet. To eliminate the risk altogether, the weight must be lost, and diabetes must go away completely to eliminate the risks.

One can certainly do regular foot inspections to avoid the worse complications of foot ulcers and be sure that their diabetes is under control. Metformin is the most used drug to treat diabetic patients but other drugs such as incretin agonists particularly GLP-1 and DPP4 inhibitors are also being used and often in combination with Metformin [13].

Some patients also use insulin injections as well. None of these drugs ensure that diabetes can be controlled at all times which makes foot inspections required.

Children can also develop foot ulcers and more and more studies are showing that the mother can contribute to these problems [14]. Cesarean sections rather than vaginal births can alter the seeding of microbiota during the birth process. In addition, the mother if she is diabetic or has elevated blood sugar, these sugars can be passed along to the infant during breastfeeding causing the infant to have elevated blood sugars [14]. Studies have been performed up to about four months of age which is the median age at which infants begin to eat solid food. Infants were divided into four groups based on cesarean versus vaginal birth and breast milk versus formula and found that vaginal births with breast milk fared better when their microbiota were compared [15]. Breast milk also contains a great number of good bacteria as well from the skin microbiota that can be missing if the mother fails to breastfeed [14]. These combinations can lead to obesity and diabetes in young children and eventually to the complications of diabetes previously described for adults including foot ulcers.

2. Incretins and diabetes

Incretins such as GLP1 and GIP are released during a meal. When one overeats, there is number of effects. Glucose and other nutrients stimulate incretin release when they are absorbed which continues to stimulate even more absorption. The nutrients are absorbed regardless of whether they are necessary for bodily functions and much of it is directed into glycolysis to eventually produce ATP, shuttled into
glycogen, or stimulated by incretins to be digested and absorbed into adipocytes and stored as fat (see Figure 1).

Incretins also stimulate the release of insulin as well and as incretin levels rise because of overeating, insulin levels rise as well. GLP-1 is released from L-cells of the small intestine [16]. One of the effects of increased secretion of insulin however can cause insulin receptors to desensitize and become nonresponsive and promoting insulin resistance. This leads to high blood glucose levels leading to diabetes. Increased amounts of insulin, incretin agonists, DTT inhibitors, and other drugs are

Figure 1.
Represented above is a simplified diagram of blood glycemic control and fat deposition. Incretins are at the heart of control and not just involved in stimulating insulin release. Incretins can have direct effects on fat deposition. In the energy balance mode and carbohydrate – insulin model of obesity it appears the influence of diet and SCFAs are not emphasized enough on the impact of glycemic control and fat deposition. Microbiota and the production of SCFAs have a profound effect on insulin release. Although carbohydrates have a large effect on secretion of insulin, other nutrients also have an effect. Although insulin can stimulate the production fat in adipocytes, incretins and SCFAs can have a direct effect as well.
designed to increase the amounts of insulin without fixing the underlying physiological causes. For TTDM and similar forms of diabetes, this is possible but for TT1 this is more difficult and in most cases impossible. So, depending on the cause, the diets and effects of microbiota are quite different.

GLP-1 and GIP both stimulate the secretion of insulin from the Beta cells of the Pancreas, yet they have different effects on obesity and fat deposition and different studies are making the functions unclear [17]. GLP-1 directly inhibits appetite and food intake and GLP-1 antagonists have been developed into drugs that can help glycemic control. GIP however lacks these functions and although some studies have used agonists to reduce weight gain, also antagonists have shown the same effect [17–20]. In addition, GIP receptor knockout mice fail to gain weight even when fed a high-fat diet [21]. GIP is released when glucose and proteins are absorbed which then promote additional absorption [22, 23].

Incretin control is what causes insulin release and increased amounts can lead to diabetes and eventually the complications that eventually lead to foot ulcers. Rises in incretins particularly GIP can contribute to weight gain by increasing absorption of nutrients and fat deposition (Figure 1). Control of incretin release could modulate and maintain controlled diabetes and less of a risk of ulcers. Even before one eats a meal, incretins such as GLP-1 and GIP are released in anticipation of glucose absorption. But the evidence is rather ambiguous [24]. Some studies show that even the sweet taste of food (even if it’s an artificial sweetener) can trigger incretin release during the cephalic phase of digestion [1, 25]. Others have shown no release of insulin during the cephalic phase [26, 27].

3. The effects of diet on diabetic foot ulcers

There are two prevailing and compelling theories of obesity and diabetes, but they are somewhat opposing theories neither of which explains entirely the complexity of obesity and glycemic control [28, 29]. The first is called the energy balance model (EBM) and the carbohydrate-insulin model (CIM). Although most scientists may be in favor of the EBM, the recent studies on the CIM and the effect and results of a low carbohydrate diet are compelling. Depending on the strategy of each model, determines the diet that would work best. Diets can influence incretin release and provide the proper amounts of SCFAs (see Figure 1).

Less than 10% of all diabetic patients have type I diabetes or similar atypical diabetic diseases. Type I diabetic patients should already be on a special diet to help control their blood glucose levels. One should monitor the intake of carbohydrates and concentrate on low glycemic foods and beverages. One should be aware that sugar-free foods and beverages do not necessarily mean carbohydrate free. Patients that fall into this category have diabetes because their pancreas beta cells do not produce sufficient amounts of insulin [30] to regulate their blood glucose levels. But there is no one meal plan that fits all. For TTDM patients, insulin insensitivity is the problem, and to relieve those symptoms usually a reduction in weight is necessary. This means a reduction in calorie intake, especially of dense energy foods such as fatty foods, and perhaps even lifestyle change.

Diabetes diets are certainly important and those that have diabetic symptoms should follow these guidelines. A carbohydrate-reduced diet is recommended but carbohydrates are found in many foods with grains such as bread, pasta, milk, any sweets that contain processed sugars, fruit, and even some vegetables that are high in
Mitigating Diabetic Foot Ulcers: The Effect of Diet and Microbiome
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starches (white and sweet potatoes, corn, peas, squash, and turnips). However, many of these foods contain many necessary nutrients and cannot necessarily be completely excluded. Most vegetables including potatoes contain vital amounts of fiber that essential bacteria that are part of the microbiota require.

Fiber is also an essential part of the diet and consists of starches that are non-digestible or less digestible than other forms of carbohydrates. In humans, cellulose and chitin are not digested like they are in ruminants such as cattle or other multi-stomach animals that consume grass or other plants. In humans, amylose even though it is a straight chain of glucose residues, and its secondary structure makes it more difficult to digest those other forms such as amylopectin that is found in plants and glycogen that is found in animals. Therefore, amylose is often considered a resistant starch, and foods that contain more amylose, and less amylopectin are considered low glycemic and will not cause glucose levels to rise as quickly or as much and can be a benefit for diabetic patients [31, 32]. Potatoes are already being developed to contain a higher amylose/amylopectin ratio by hybridizing with other strains while at the same time increasing their protein and amino acid content [31]. Not all of these new plants are commercially available as yet and potatoes such as huckleberry gold although available are more expensive than the more common commercially available varieties. Although these potatoes have been reported to have higher amylose/amylopectin ratios, it still remains to be seen if the cooking methods will have an effect and if the varieties will taste good enough to be accepted as substitutes. Until then, the recommended foods include Grains, beans (canned baked beans tend to have sugars added), rice, pasta, and starchy vegetables are actually recommended because of their high fiber content even though they may not be low glycemic.

In addition, it is rapidly becoming more important to consume vegetables because of their high polyphenol content as well. Polyphenols are a large group of plant metabolites that have many medicinal properties including antidiabetic effects. Polyphenols have been shown to decrease blood glucose levels and increase insulin secretion and sensitivity [33, 34].

The release of digested carbohydrates releases glucose that is absorbed which can raise blood glucose levels. Proteins and fats have not been found to affect diabetic patients, but any weight gain can contribute to diabetes and insulin resistance. Type one diabetes does not typically cause insulin resistance, but some type one diabetic patients have become overweight, and more than a third now have an increased risk of chronic kidney disease [35]. It has been shown that the increased blood glucose levels damage the delicate blood vessels, and many develop high blood pressure as well which can damage the vessels as well [30], which could contribute to insulin resistance. Since there is no one diet fits all, the current diet for a particular individual depends on age, weight, and the activity of the individual. It is suggested that a registered dietician may be the best way to design a diet. Typically, an individual should not consume more than 2000 calories per day, and no more than half should be from carbohydrates. Typically, also one gram of carbohydrates has about 4 calories, but these are only estimates. There are general guidelines for patients with diabetes. Watching portion size and calories are recommended for any diabetes diet. Reducing the intake of fried foods, sweets, salts and fats is a part of any diabetes diet. In some cases, even eating less more often can stabilize your glucose levels in the blood. One thing however to keep in mind is that not all calories are the same. Calories coming from energy-dense diets will predispose individuals to weight gain irrespective of the nutrient content of the food consumed [36, 37].
3.1 The ketogenic diet

The most popular of diabetes-related diets are the ketogenic diet. Ketogenic diets are frequently higher fat, lower fiber diets that have lower carbohydrates making it easier to control diabetes and induce weight loss [37–39]. Low fiber diets, however, will not restore normal microbiota which contributes to obesity therefore it is not a long-term solution that should be discontinued once the normal weight is achieved. There are different forms of these diets but essentially even less carbohydrate is consumed in favor of additional protein. This is known as nutritional ketosis which is a normal biological process that may in fact reduce weight and eventually be beneficial to the individual [37, 38]. But it would only be normal when the diabetes is under control and blood glucose levels are normal. However, this is different than ketoacidosis which can occur in diabetic patients where the diabetes is not under control when insulin levels are too low, and glucose cannot be absorbed into cells instead the body uses fats for fuel. In this case, there is a sharp unhealthy rise in ketones in the blood which in turn causes the blood to become more acidic [38]. This condition can be fatal if not treated. Keto diets as well can lead to nutrient deficiencies in calcium, magnesium, vitamin D, and folic acid. The vast majority of TTDM patients are obese and only when their obesity is also under control and reduced will their diabetes symptoms disappear [37, 38]. Nevertheless, long-term use of the ketogenic diet has not been well studied and can have serious side effects. It has been shown that this diet while preventing some cancers can cause renal cancer and tumor growth in integument and other epithelial tissues [38, 40]. Ketogenic diets are often high in fat and low in fiber. That kind of diet will cause LDL levels to rise to lead to serious heart and cardiovascular diseases such as atherosclerosis. If the fats are reduced in favor of higher protein levels that can lead to serious kidney diseases and kidney stones [37].

Type one diabetes and TTDM patients can both benefit from a ketogenic diet, but the endpoints will be different. For TTDM patients, a ketogenic diet could restore normal weight and therefore usually relieve the symptoms of diabetes. For type one, the risk of ketoacidosis is significantly higher and so needs more careful monitoring. The Ketogenic diet can benefit diabetic patients because it reduces the glucose levels in the blood, lowers blood pressure, and can contribute to weight loss [37, 39].

4. Other diets

4.1 The low-carb diet

A low-carb diet is different than the ketogenic diet because it is less limiting in the amount of carbohydrates. You don't have to give up carbohydrates because you have diabetes. Atkins or South Beach are low-carb diets that are easier to comply with, and many patients still benefit from them. Studies show that this diet could be the first step in managing the disease [41].

4.2 Mediterranean diet

This diet promotes fruits and vegetables as well as fish, chicken, nuts, olive oil, legumes, and whole grains with a reduction of red meat, butter, and salt. Studies have shown that diet can help keep blood sugar levels under control. You can have some alcohol with meals as well [42].
4.3 Dash diet

Dieticians recommend this eating plan usually as a way to control hypertension. The diet consists of fruits, vegetables, low-fat dairy, whole grains, lean meats, fish, nuts, and beans. (It does allow for some sweets in moderation.) Studies have found that it can improve insulin sensitivity when it is part of an overall weight loss program with exercise [43].

4.4 Zone diet

Meals are designed to contain 40% carbs, 30% protein, and 30% fat. Carbs are ranked as good or bad based on the glycemic index. Foods like chicken and barley are recommended but not potatoes and egg yolks. Studies have found it had a positive effect on glycemic control and waist size, so it may be a good choice. Ask your doctor about it (zonediet.com).

4.5 Paleo diet

The idea behind this diet is to eat the way early humans did before modern farming. The diet consists of no dairy, refined sugar, grains, or legumes, and no processed vegetable oils like soybean oil or canola oil. You can have fruits and vegetables, lean meats (preferably grass-fed), fish, nuts, and seeds. Using this, diet studies show this eating strategy can improve blood sugar and diabetes (thepaleodiet.com [44]).

4.6 Vegetarian/vegan

Limiting or avoiding animal products like chicken, fish, and yogurt may be a healthier way to live for some individuals. However serious deficiencies in nutrients can occur. The diet generally restricts meat and poultry but in some cases, dairy, eggs, or fish are allowed to prevent these deficiencies (Mayo Clinic; Vegetarian Diet: How to get the best nutrition). Research shows that people who eat a plant-based diet get more fiber and take in fewer calories and fat than nonvegetarians. This would bring diabetes under control and restore the normal microbiota balance however deficiencies in Vitamin B12, Omega 3 fatty acids, iron, zinc, and iodine can develop if the diet is not properly monitored.

5. Microbiota

The large intestine (colon) is populated by a large number of bacterial, archaeal, protozoan, viral and fungal species that are collectively known as the gut microbiota. The number of species ranges from hundreds to tens of thousands that outnumber the human genome by at least 100:1 and are known as the second human genome. The microbiota, especially the bacterial species, forms a community of organisms that metabolize nondigestible carbohydrates, plant cell wall material, and other oligosaccharides that make up dietary fiber, and they produce a wide variety of metabolites including short-chain fatty acids (SCFAs) [45]. Other substances, especially the polyphenols in the diet, serve as substrates for the microbiota. Other secondary molecules include vitamins, cholesterol, and their derivatives, along with the other remaining cell wall components such as lipopolysaccharides, which can also be found
as metabolites formed by the microbiota [46]. A high fat, low fiber diet reduces SCFAs producing increasing the numbers Firmicutes and decreasing the numbers of the Bacteroidetes phyla, and also decreasing the level of SCFAs (since there is less fiber) and the synthesis of other essential metabolites [47]. SCFAs such as acetate, propionate, and butyrate are synthesized as byproducts of resistance starch metabolism by the microbiota. On the other hand, these bacteria can also metabolize histidine into imidazole propionate which actually can modulate host inflammation, metabolism and cause insulin resistance [48].

To a certain extent, antibiotics, certain diseases (e.g., inflammatory bowel diseases; IBD), and the genetics of the host may contribute to dysbiosis; however, an individual's diet has a major impact on the growth and maturation of the microbiota [49]. SCFAs have distinct effects on colon epithelia, specific transport and signaling mechanisms, and profound effects on a human's health including diabetes.

5.1 The chemistry and metabolism of SCFAs

SCFAs are mostly aliphatic carboxylic acids that have a carbon chain of six or less. A few SCFAs are branched and synthesized from various amino acids but contribute only about 5% of the overall SCFAs produced.

The microbiota consists mainly of Bacteroidetes and Firmicutes (combined are approximately 90% of the gut microbiota), while the remaining bacteria consist of Actinobacteria, Proteobacteria, and Verrucomicrobiota. Amazingly, even within the first month of life, the gastrointestinal (GI) tracts of children are colonized by different species of Bacteroidetes and Firmicutes at a much lower level. A child's GI tract begins germ-free but accumulates additional numbers of species until the child achieves adulthood. Diet, geographic location, and the genetics of the individual are all contributors to the microbiota colonization of the adult GI tract. In addition, it is now hypothesized that microbiota present in the birth canal during childbirth contributes to gastrointestinal colonization and those children born through the Cesarian section have more health problems than those who do not. Breastfeeding rather than simple formula (not exactly the same diet) also modulates the microbial species that colonize the GI tracts since breastmilk has bacteria from the skin microbiota. Therefore, it is conceivable that the diet can have a profound influence on the child's microbiota population and health. It is even more conceivable that an increase in childhood obesity could be influenced by changes and/or deficits in the developing microbiota [49–51].

Nondigested carbohydrates that are used as nutrients by the microbiota of the GI tract are referred to as prebiotics [52]. Enteric nutrition is given to certain patients as a supplement during their hospital stay to prevent malnutrition. Such treatments frequently result in diarrhea. Once prebiotics are added to the enteric nutrition, the symptoms of diarrhea disappear [53]. Thus, a diet with a proper prebiotic level is critical for maintaining a proper Firmicutes to Bacteroidetes ratio. Conversely, a high fat, low fiber (i.e., low prebiotic) diet will increase the Firmicutes to Bacteroidetes ratio [49]. It is well known that SCFAs are produced by the microbiota and when they are absorbed, the SCFAs stimulate Na+/water absorption [54]. Therefore, prebiotics are essential to maintain a proper ratio for any diet. Prebiotics are those foods that contain different types of nondigestible fiber as a fuel source for microbiota. The prebiotics include mostly vegetables such as artichokes, leeks, garlic, onions, asparagus, wheat bran/flour, bananas, and chicory root. It is important to note that when vegetables are cooked they lose at least a third of their fiber content [52].
Once SCFAs are produced, most are transported into colonocytes and are metabolized by the colonocytes as a nutrient for cell growth and metabolism. Very little of the SCFAs are transported into the systemic circulation. Acetate levels are likely high enough to have effects on the other organs, but very little if any, butyrate or propionate is thought to leave the portal blood and liver [55]. A limited amount is produced and absorbed in the small intestine, but the colon is certainly the major source [56]. Receptors for SCFAs exist in most of the major organs including the gastrointestinal tract. In the intestine and colon, SCFAs are linked to motility and maintenance of the epithelial barrier. SCFAs stimulate water absorption, while at the same time increasing motility, maintaining the epithelial barrier and therefore preventing constipation and diarrhea [57]. When entering into the systemic circulation, SCFAs also have profound effects on whole body health and metabolism. SCFAs are the source of fuel for the heart and the cardiovascular system, they control body weight and insulin release, and are precursors for lipid and glucose production in the liver (gluconeogenesis). Commensal bacteria have a number of health benefits which include the development of the gastrointestinal tract and other tissues such as the central nervous system, maintaining the immune system, and increasing metabolism [58]. Therefore, an imbalance or dysregulation of microbiota populations could disrupt normal metabolism and water balance and result in obesity, diabetes, and its symptoms and complications such as foot ulcers.

The major SCFAs produced are acetate (C2), propionate (C3), and butyrate (C4) which contain two, three, and four carbons, respectively. These SCFAs are mainly synthesized by the Firmicutes species Lactobacillus and also the Actinomycetota species Bifidobacteria. Bacteroidetes bacteria can also produce SCFAs but at lower levels. The SCFAs act as the primary source of energy for colonocytes. Different species of bacteria with different metabolic steps are responsible for the formation of each of the SCFAs. None of the bacteria have all of the necessary enzymes to produce all three of the SCFAs directly from dietary fiber. Nondigestible carbohydrates enter the citric acid cycle of bacteria at different points in different bacteria. Propionate is formed from succinyl-CoA, an intermediate of the citric acid cycle, as well as lactate and propanediol. Acetate and butyrate are formed from acetyl-CoA [59, 60]. In addition to entering the citric acid cycle and being used as an energy source, SCFAs also have profound epigenetic effects to increase the rate of gene transcription by inhibiting histone deacetylase (HDAC) activity [61]. The SCFAs affect many genes that regulate transcription and colonocyte homeostasis [62, 63]. These accumulated epigenetic events are thought to increase the incidence of colorectal cancer [64, 65]. Butyrate is synthesized from acetate, while propionate is synthesized by butyrate-producing bacterial species such as Faecalibacterium, Eubacterium, and Anaerostipes [66, 67]. Additionally, to absorption (i.e., about 95% of SCFAs produced), some of the SCFAs are excreted in the feces [60]. The amount of SCFAs produced can vary greatly by the content and type of dietary fiber, and the number and species of bacteria. Other factors such as antibiotics, bypass surgery, and stress can also alter the microbiota species composition and SCFAs production. Local sanitation and the introduction of microbes into the diet determine whether the proper microbiota is developed in the GI tract. Amazingly, people in countries with the best sanitation introduce fewer microbes into the microbiota, which consequently leads to dysbiosis and diseases such as obesity and diabetes [49].

SCFAs can exert physiological function either during transport across the colonocytes or by binding to their receptors located on the gastrointestinal mucosa. A number of orphan G-protein-linked receptors were discovered and initially had no
known ligands [68]. However, later studies demonstrated that SCFAs activated several of these G-protein-linked receptors, and several of them are identified to present in the mucosa of intestine and colon [69]. They include the G-protein coupled receptor (GPR) GPR43 (acetate and propionate) and GPR41 (propionate and butyrate), which have about 40% homology across species [70]. GPR43 and GPR41 are also known as free fatty acid receptors, (FFAR) FFAR2, and FFAR3, respectively. Acetate and propionate are ligands for GPR43 (FFAR2), while propionate and butyrate are ligands for GPR42 (FFAR3) [45]. Butyrate also binds to GPR109a, which is distributed along the colon, T-cells, and the microglia. GPR43 is highly expressed in immune cells, adipose tissue (stimulates fat deposition), distal ileum (increases motility, and stimulates peptide-YY (PYY) and glucagon-like peptide-1 (GLP-1) secretion), skeletal muscle, and the heart [71] that are tissues all involved in diabetes and obesity. Therefore, during dysbiosis and diabetes when there is a lack of SCFAs this could contribute to a decrease in immune responses and cause cardiovascular disorders. The main function of GPR43 is to maintain energy homeostasis within the body, GPR43 increases energy released by improving glucose tolerance and increasing energy utilization within the body [72]. GPR43 is also present in pancreatic \( \beta \)-cells and stimulates insulin secretion, which in turn increases glucose absorption into the tissues to aid increased energy utilization. These aspects were demonstrated using GPR43 knockout mice [73, 74]. Therefore, when SCFAs are not synthesized in sufficient quantities then that would result in difficulties in maintaining normal energy homeostasis and glucose utilization. Although most of the SCFAs are utilized in the colon, more dietary fiber consumption, resulting in greater amounts of SCFAs, gets absorbed into the systemic circulation and thus interacts with other tissue receptors. Although further studies are required, it is likely that SCFAs increase body metabolism, as high fiber diets result in weight loss and reduce blood lipid levels. Additionally, increases in HDL levels are observed, which lowers the chances of atherosclerosis, but an increase in blood cholesterol levels has been shown in some studies [47, 75–77]. However, this reported evidence indicates that SCFAs activate receptors that release GLP-1 and increase insulin secretion to regulate blood glucose levels [70]. In the pulmonary system, SCFAs protect against inflammation by activating the GPR41 and reducing hematopoiesis and infiltration of immune cells [78]. Loss of these functions would result in weight gain, cardiovascular disorders, and insulin resistance.

Altered microbiota populations have been detected in several diseases including obesity and conditions resulting from the overuse of antibiotics. The overuse of antibiotics has been shown to decrease Bacteroidetes and increase Firmicutes [14]. Metabolic activity of Bacteroidetes and Firmicutes taxa determined by 16s RNA analyses revealed that the Firmicutes tend to be more active than that of Bacteroidetes taxa. Even with the cessation of antibiotic treatment, some species, mainly Firmicutes, never return to normal levels [76, 79]. When microbiota utilize fats and metabolize less fiber in the diet, the microbiota synthesize fewer SCFAs but also produce metabolites that contribute to obesity. When the ratio of Firmicutes to Bacteroidetes increases that contributes to an increased risk of diabetes and obesity [80]. However, a change in the ratio does not always lead to diabetes [81, 82] because there can be regional differences in the expression of the microbiota in lean and obese individuals which likely depends on the diet at that locale [83, 84]. However, dietary requirements for modulation of diabetes may not have enough impact but it is certainly important since increases in fiber in the diet reduced the symptoms of diabetes in patients [80, 85]. Many of these food items rich in fiber also contain large amounts of sugars and carbohydrates. It is interesting that
with weight loss comes changes in microbiota, but the research design many times do not reflect enough which came first, the change in weight or the change in microbiota making interpretation of results difficult.

There are two major phyla of bacteria that are present in the gut microbiome. The ratio of these bacteria is balanced in healthy lean individuals. Firmicutes are considered to be the “bad” bacteria but they are the major phyla that produce the short chain fatty acids needed as a fuel source for the colon [86, 87]. Without the SCFA when the Bacteroidetes become the dominant phyla with fewer Firmicutes colon will become more permeable to bacterial infections and diseases such as Inflammatory Bowel Disease although some report even Bacteroidetes are also reduced [88]. Other phyla include Actinobacteria as they increase significantly decrease the risk of developing diabetes [89], Proteobacteria increases have been linked to dysbiosis and may not cause diabetes but those with diabetes have increased amounts, particularly in TTDM [90], and Verrucomicrobia is also increased in diabetic patients [91].

High fat low fiber diets tend to diminish and cause dysbiosis of the colon microbiota. Fermented foods are considered to be among the best foods that can replace or restore the normal balance of microbiota in humans [14]. Yogurt is considered to be among the best, but only recently have there been any definitive studies. Bifidobacterium animalis and Lactobacillus species are said to be the most beneficial and are found in yogurt and other fermented milk products [14, 92]; however, immune deficient patients should avoid yogurts and other fermented milk products since they could be susceptible to a fatal form of septicemia [93]. These short-chain fatty acids (SCFAs) are not just linked as a fuel source for colonocytes in the large intestine but also to proper immune responses and proper intestinal permeability to prevent bacterial infections [88]. Parasitic infections which can result from increased permeability such as toxoplasmosis, hydatidosis, and cysticercosis infect a large population worldwide. Toxoplasma gondii in the pancreas could damage the pancreatic cells. Hence, insulin secretion would be affected which leads to an increased risk of diabetes [94].

6. Other microbiomes

The gut microbiome is by far the most important when it comes to diabetes and obesity, but it is becoming clear that other microbiomes may have effects as well. Small intestinal bacterial overgrowth syndrome (SIBO), Helicobacter pylori, and the oral microbiome are now thought to contribute as well. SIBO and H. pylori are often comorbidities for diabetic patients.

SIBO is an upset of the natural balance of microbiota in the small intestine. It can be the result of enteric nervous system disorders such as IBS and because of nausea and abdominal pain usually result in weight loss, loss of appetite, bloating and diarrhea, and malnutrition. SIBO causes increased blood glucose levels and insulin resistance and worsening glycemic control [95]. Other investigators though believe that it is diabetes that causes SIBO. About a third of diabetic patients also have SIBO. [96] and is diagnosed by a simple hydrogen breath test. However, unless the SIBO can be controlled, these patients will have greater difficulty in controlling their diabetes and will have a higher risk of foot ulcers [96].

Helicobacter pylori infections in the stomach also increase the likelihood of TTDM. Causal contact and contaminated food or water can transmit the disease. It is believed
that the infections cause the release of gastric hormones and gastrointestinal inflammation that leads eventually to insulin resistance and diabetes [97].

Oral microbiomes are now being examined and studies show that this microbiome is also involved in the progression of diabetes and obesity. *Actinobacteria* levels are seriously depressed in diabetic patients and *Firmicute/Bacteroidetes* ratios have increased just as in gut microbiota in TTDM patients [89, 98, 99].

7. Host genetics

Genetics can affect many areas of human physiology that can affect the progression of diabetic foot ulcers. There are genes that can affect not just obesity but also diabetes. As many as 20 different genes have been associated with type I diabetes [100]. It is usually an autoimmune disease passed on from parents to offspring. However, there is a greater chance of parents having children who also have Type 1 Diabetes however there is no evidence that it's not simply due to similar diets and living conditions since they are likely to live all in the same place. For type two diabetic patients the atypical types have been directly linked to mutations in certain genes but that only accounts for a small percentage of diabetic patients. MODY type diabetes is all the result of a single mutation causing a lack of glycemic control [12]. Nevertheless, some investigators believe that genes only predispose an individual to obesity and do not guarantee the condition and that environment plays just as important a role in diabetes/obesity phenotype. Now, there is also evidence that *Firmicute* family *Christensenellaceae* increased in numbers in lean non-diabetic individuals and is directly associated with the host genome [101]. It was demonstrated that in identical twins, the microbiota was more similar than twins that were not identical [102] which suggests genetics has an important role in determining correct balance of microbiota and therefore maintenance of energy balance, proper weight, and glycemic control.

8. Conclusion

Diabetic foot ulcers have protocols for treatment and prevention but ultimately the only way to prevent them entirely is to address the diabetes of the patients involved. Although this review is not entirely a comprehensive review of diabetes, it is clear that its prevention is not a simple matter especially if its cause and treatment are not necessarily well defined. Since there are two prevailing theories of its cause and there are different types of diabetes and diets the effects of microbiota and diet are not going to be the same for everyone. Figure 1 is a simplified diagram of all the players. Microbiota and Diet have a great influence on incretin action and glycemic control but SCFA, incretins, and insulin all have direct effects on the deposition of fat in adipocytes. Not listed in Figure 1 is that glucose itself can be synthesized into fats. Incretins can affect glucose metabolism by turning glucose into fats especially when the insulin levels are high.

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