Dietary Fibers and Intestinal Microbiota Affects T2D

Subjects: Microbiology

Contributor: Muhammad Mazhar, Yong Zhu, Likang Qin

Foods contain dietary fibers which can be classified into soluble and insoluble forms. The nutritional composition of fast foods is considered unhealthy because it negatively affects the production of short-chain fatty acids (SCFAs). Dietary fiber is resistant to digestive enzymes in the gut, which modulates the anaerobic intestinal microbiota (AIM) and fabricates SCFAs. Acetate, butyrate, and propionate are dominant in the gut and are generated via Wood–Ljungdahl and acrylate pathways. In pancreatic dysfunction, the release of insulin/glucagon is impaired, leading to hyperglycemia. SCFAs enhance insulin sensitivity or secretion, beta-cell function, leptin release, mitochondrial function, and intestinal gluconeogenesis in human organs, which positively affects type 2 diabetes (T2D). Research models have shown that SCFAs either enhance the release of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) from L-cells (entero-endocrine), or promotes the release of leptin hormone in adipose tissues through G-protein receptors GPR-41 and GPR-43. Dietary fiber is a component that influences the production of SCFAs by AIM, which may have beneficial effects on T2D.

Keywords: dietary fibers ; intestinal microbiota ; short-chain fatty acids ; fermentation

1. Dietary Fiber, Inflammatory Markers, and Type 2 Diabetes (T2D)

T2D is among the major diseases associated with a low level of inflammatory processes, characterized by amendments in the secretion of cytokines [1]. The amount of inflammatory markers (IL-6, TNF-α, and LPS) in T2D is increased, which is associated with dysfunction in insulin resistance and β-cell activity, and the amount of LPS in diabetic patients is twice as high as that in healthy individuals [2]. A high-fat diet is associated with metabolic endotoxemia caused by serum LPS, resulting in obesity and insulin resistance [3], and high serum LPS enhances TNF-α and inhibits insulin signals [4]. An excess amount of ANK-α indirectly inhibits insulin signaling by serine-307 phosphorylation in the substrate of the insulin receptor [5]. According to scientific reports, the composition of the diet can positively affect the inflammatory process; *Lactobacillus* spp. and *Bifidobacterium* spp., which are stimulated by dietary fiber, show anti-inflammatory properties [6]. Dietary fiber at 40 g/day can reduce the level of TNF-α [7].

2. Effects of Fructose on SCFAs and T2D

Sugar is an important source of energy in the daily diet, and there is increasing evidence that high sugar intake causes a number of major diet-related health problems, such as T2D and obesity [8][9]. Dietary factors influence blood glucose homeostasis in T2D; blood glucose levels rise when fructose is converted into glucose in the liver. This conversion takes time, so a small portion of fructose is converted into glucose, resulting in a lower increase in blood glucose levels [10]; therefore, the glycemic index of fructose is only 23 [11]. In addition to contributing to blood glucose homeostasis, fructose has also been shown to improve glycemic control at moderate levels [12][13]. The health effects of fructose are closely related to the consumption amount. Ultimately, it was determined that a high-fructose diet and a certain gut microbiota profile may be associated with the inflammation of the liver, pancreas, and colon. With low or inadequate fructose intake, no adverse effects were found on body weight, fasting blood glucose, histology, gut microbiota, or colonic SCFA levels [14][15][16]. Some evidence showed that fructose causes insulin resistance in the liver, which can negatively impact blood glucose homeostasis [17].

3. Effects of Lipids on SCFAs and T2D

A lipid molecule is mostly made up of repeating units named fatty acids. There are two types of fatty acids, saturated and unsaturated. Humans get most of their energy from fatty acids, which are the main components of triacylglycerols found in oils and fats [18][19]. Long-term consumption of a high-fat diet affects gut microbiota composition in animal models as well as in humans, which directly impacts SCFA production and host health [20]. High-fat diets containing medium-chain fatty

acids, monounsaturated fatty acids, and polyunsaturated fatty acids, low-fat diets containing long-chain fatty acids, and diets with high Bacteroidetes or Firmicutes ratios were associated with increased SCFA production [21].

4. Short-Chain Fatty Acids (SCFAs)

SCFAs are organic acids produced in the human gut, where the AIM resides [22]. Quantitatively, these fatty acids are measured in millimoles, and they are predominately represented by acetate, butyrate, and propionate [23]. These three SCFAs are discussed here. The dietary carbon flow is based on SCFAs [24], and their production is fairly well understood and characterized [25][26]. The ratio and concentration of SCFAs depend on the microbial composition and the substrate (dietary fiber) provided to the GM [27]. The molar ratio of acetate, propionate, and butyrate is 3:1:1. SCFAs constitute 90–95% of the colon, whereas formic acid is present in a smaller proportion [23]. As a result of antibiotic treatment depleting the microbiota, mice were found to produce lower amounts of SCFAs, compared to mice that did not receive antibiotics [28]. A diet rich in prebiotics may be particularly effective at increasing SCFA production in diabetes [29]. According to previous studies, individuals with T2D have lower proportions of microbiota species producing butyrate [29][30].

4.1. The Contribution of Gut Microbiota Producing SCFAs

Dietary fibers are resistant to gut digestive enzymes, which contribute to the production of SCFAs during colonic fermentation [31]. Acetate, propionate, and butyrate are dominant SCFAs in the gut [6]. These fatty acids are composed of 1–6 carbon atoms and are naturally saturated [32]. Present-day research has shown a significant role for AIM, and the metabolites produced during dietary fiber fermentation positively contribute to T2D [33]. Gut intestinal microbiota, including *Clostridiales* spp. SS3/4, *Roseburia inulinivorans*, *Roseburia intestinalis*, *Faecalibacterium prausnitzii*, and *Eubacterium rectale*, produce butyrate, which has a protective role in T2D, even though these species are decreased in diabetes [34]. In addition, oral administration of *Clostridium butyricum* in obese diabetic rats was found to modulate gut microbiota to produce butyrate, leading to reduced proportions of Bacteroides and Firmicutes spp. [35].

In diet-induced diabetes, chitosan and antibiotics targeting Gram-negative intestinal microbes may be considered antidiabetic agents [36][37]. Cross-feeding GM metabolizes lactate into acetate, propionate, and butyrate in the gut fermentation process, in which propionate and butyrate are produced in limited quantities owing to selected GM, while acetate is a regular product in the gut [24]. Propionate is produced during the fermentation of propiogenic substrate (fucose/rhamnose) by *Akkermansia municiphilla*, whereas butyrate is produced through RS fermentation by *Eubacterium hallii*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Ruminococcus bromii* in the gut; moreover, butyrogenic bacteria ferment pyruvate, lactate, and acetate into butyrate [23]. Acetate, propionate, and butyrate are the energy sources for the human body. Butyrate is directly utilized in the liver, heart, brain, and colon; propionate is used for gluconeogenesis in the liver, and acetate is used as fuel in peripheral tissues [38].

The responsiveness of free fatty acid receptors (FFAR-2 and -3) is proportional to the length of the carbon chain. For example, acetate and propionate are more responsive to FFAR-2, whereas butyrate and propionate are more responsive to FFAR-3 [39]. Medium (FFAR-1) and long-chain (FFAR-4) fatty acids were found to positively respond to inflammation and insulin secretion [40]. FFAR-1 enhances specific pancreatic β-cell activity, while in T2D, this activity is downregulated, resulting in FFAR-1 inhibition and insulin resistance [41]. FFAR-4 boosts these fatty acids (unsaturated) to stimulate glucagon-like peptide-1 (GLP-1), secreting insulin from β-cells [42]. Propionate and butyrate may positively regulate obesity and T2D when administered orally [43][44][45].

4.2. Production of SCFAs via Anaerobic Bacterial Pathways and the Role of Akkermansia Muciniphila in T2D

The non-digestible carbohydrates are hydrolyzed by the AIM into monosaccharides and oligosaccharides during anaerobic fermentation in the colon [46]. For the metabolization of monosaccharides into phosphoenolpyruvate (PEP), the Embden–Meyerhof–Parnas pathway (sugars containing 6-c) and the pentose phosphate pathway (sugars containing 5-c) are utilized [25]. Eventually, organic acids/alcohols are formed during PEP fermentation. Nicotinamide adenine dinucleotide (NAD) + hydrogen (H) (NADH) is produced during the reaction of an acidic protein, glyceraldehyde-3-phosphate dehydrogenase (GAPDH). First is the traditional fermentation pathway, in which lactate/ethanol is produced from the reduction of pyruvate. Second, pyruvate is reduced to acetyl-CoA (ACA) and NADH to NAD^+ [47]. The second pathway produces excess amounts of H_2 molecules by using two major routes, pyruvate (exergonic) and NADH (endergonic) via ferredoxin oxidoreductase and hydrogenase, respectively. Despite depleting/consuming H_2 molecules, the AIM is a primary participant in the fermentation process when H_2 pressure in the large intestine (lumen) is low [48]. Third, the fundamental electron transport chain (ETC) proceeds with anaerobes, starting with PEP carboxylation and the reduction of oxaloacetate into fumarate [49]. The electrons are accepted by fumarate from NADH; NADH dehydrogenase and

fumarate reductase constituted an ordinary electron transfer chain (OETC) [49][50]. NADH-dehydrogenase contributes to the transport of protons across the cell membrane, resulting in the chemiosmotic synthesis of ATP. Succinate (produced by fumarate reductase) is transformed into methylmalonate once the preferential load of CO_2 is reduced. PEP can also be recycled from oxaloacetate through the carboxylation process.

SCFAs are the end product of the fermentation pathways. Pyruvate is transformed into ACA, releasing H_2 and CO_2 molecules. Hydrolysis of ACA leads to the formation of acetate, or it can also be produced by the Wood–Ljungdahl pathway utilizing CO_2, wherein CO_2 is reduced to CO coupled with CoASH and a methyl group and converted to ACA [51][52]. Propionate is formed either by utilizing PEP via OETC or by reducing lactate to propionate via the acrylate pathway [25]. These pathways accommodate supplementary NADH associated with lactate fermentation. The condensation of ACA (2 molecules) results in the formation of butyrate, which is subsequently reduced to butyryl CoA. ACA is produced from lactate, and then lactate is utilized by gut bacteria to produce butyrate [53]. Two pathways are involved in the formation of butyrate: the traditional pathway uses phosphotransbutyrylase and butyrate kinase to convert butyryl CoA into butyrate, accompanying ATP formation, and in the alternative pathway, butyryl CoA is converted to butyrate via butyryl-CoA: acetate CoA transferase [54][55]. The exogenic utilization of acetate to form butyrate and ACA involves cross-feeding among acetate and butyrate-producing bacteria [56][57]; the human GM prefers the alternative over the traditional pathway [54].

The symbiotic association between GM and the human body is significant in SCFA production [58]. The primary metabolites (H_2 molecules) produced to get acetate must be utilized by secondary fermenters to reduce the burden of these molecules and accelerate the oxidation of NADH via primary fermenters [59]. The human body provides the CO_2 molecules required in the OETC, and an average of 0.7 kg/day of CO_2 is produced by the human organism [60]. By exchanging SCFA anions, some of that production is secreted into the gut (lumen) as HCO_3, which is likely a significant pH-regulating mechanism, since protons in the gut (lumen) generated during the formation of SCFAs are neutralized by bicarbonate to produce CO_2 [59]. Subsequently, much is known about the biochemistry of SCFA production from carbohydrates via the AIM. However, further study is still needed to determine whether SCFAs, as the significant output of indigestible carbohydrates via the AIM, have beneficial effects in T2D.

Akkermansia muciniphila is the only representative Gram-negative *Verrucomicrobia* inhabiting human intestinal mucosa [61]. In the studies by Derrien, gene sequence analysis revealed that multiple genes are associated with mucin encoding, and a single chromosome containing 2176 genes with 55.8% GC content was found in the MucT type strain of *A. muciniphila* (ATCC BAA-835 1/4 CIP107961T) [62][63]. This immobile, oval-shaped microorganism is purely anaerobic and contains chemical organotrophic material that can endure low levels of oxygen. The enzymes produced by *A. muciniphila* were responsible for the breakdown of mucin, and the mucin in the mucosal layer of the epithelium was used as a source of carbon and nitrogen. In order to release the sulfate, *A. muciniphila* splits these compounds into acetic and propionic compounds [64][65]. According to an analysis of its 16SrRNA signature, *A. muciniphila* makes up 3 to 5% of the gut microbiome even in healthy adults, but the amount depends on several factors. Age has been closely associated with stability in humans. This species begins to colonize at a young age and ranges from 5.0 to 8.8 log cells/g in a year, which is comparable to the adult stage, although it decreases with age [66][67]. The combined effects of an excess amount of *A. muciniphila* supplementation can positively affect metabolic disorders including T2D, and early vancomycin therapy may help control the progression of autoimmune diabetes by early colonization of the intestinal tract with *A. muciniphila* [68][69].

4.3. Effects of SCFAs on T2D

SCFAs are metabolites of gut microbe fermentation that result from indigestible dietary fiber and may have a beneficial role in T2D [70]. Compared to normal animals, diabetic rodents that consumed a high-fat diet with streptozotocin showed lower levels of acetate, propionate, and butyrate [71][72]. It was found that T2D patients had lower fecal butyrate and propionate concentrations, as well as acetate concentrations, than healthy subjects [73]. Improved insulin secretion/sensitivity, reduced fat accumulation, intestinal gluconeogenesis (IGN) triggering, and inflammation are the mechanisms by which SCFAs can positively affect T2D [22][74]. A study using homeostatic model assessment of insulin resistance (HOMA-IR) observed an adverse correlation between blood insulin levels and total SCFAs, including acetate and propionate [75]. In vitro and in vivo studies showed that propionate can enhance the release of glucose-stimulated insulin, sustain β-cell mass by decreasing trans-differentiation in α-cells, obstruct apoptosis, and assist in proliferation [22][76]. Moreover, it was shown in mouse models that butyrate improved insulin sensitivity [44][77]. These mechanisms support energy consumption and boost mitochondrial functions [44].

Propionate- or butyrate-induced IGN affects glucose homeostasis, the cAMP-dependent pathway, and the gut–brain neural circuit [78]. Acetate enhances the suppression of lipogenesis in the liver and decreases lipid aggregation in adipose tissues, while glucose transporter-4 genes and myoglobin are enhanced in the abdominal muscles of diabetic rats [79]. The

peroxisome proliferator-activated receptor-α (PPAR-α) gene was upregulated in the presence of acetate, which may suppress body fat aggregation [80][81][82]. Furthermore, SCFA supplementation reduces hepatic steatosis and body weight [83]. In vitro and in vivo models showed that SCFAs either enhance the release of peptide YY (PYY) and GLP-1 from L-cells (entero-endocrine), or promote the release of leptin hormone satiation in adipose tissues through G-protein receptors (GPR-41 and/or GPR-43) [84][85][86][87]. SCFAs promote lipid oxidation and energy consumption and were found to increase fasting fat oxidation and PYY concentration during colonic infusion in obese subjects [88]. Butyrate may weaken inflammation generated by the interaction of macrophages and adipocytes by decreasing lipolysis and obstructing inflammatory signals [89]. These fatty acids showed beneficial effects on T2D by reducing the production of TNK-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1); nuclear factor kappa-B (NF-κB) activity was also constrained. Propionate had a positive influence on T2D, participating in the downregulation of inflammatory chemokines and cytokines, such as CC chemokine ligand-5 (CCL-5) and TNF-α [90].

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