Nutrition modifications of gut microbiota in type 2 diabetes.

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Abstract

The human gut microbiome is composed of 100 trillion microorganisms that create complex foreign to local interactions. Current research suggests variability of microbes relevant to type of subject (i.e. humans, mice), gravity of disease, age, glucose intake or weight of subjects. The goal of this review is to determine the role of nutrition in human gut microbiota of type 2 diabetics, determining the causative, preventative and correlative role of microbe-host interaction in type 2 diabetes and seeking interventions to prevent toxic formation of microbes. Sufficient data will be closely examined, including research methodologies studies, advanced techniques utilized in the interface between human gut microbiome and diabetes. Nutritional intake accounts for 57% in the alteration of intestinal integrity and diabetes development while genetics only accounts for 12%. Therefore, scrutinizing dietary behavior is crucial in determining the formation of diverse microbiome. According to studies present, we conclude that probiotics are immensely correlated with preventing T2D. Carbohydrates had dual role, positive and negative in modulating inflammatory processes that cause T2D. Complex Carbohydrates positively modulated T2D through short chain fatty acids. High fatty acids such as omega-6 polyunsaturated fatty acids decreased pro-inflammatory cytokines which inhibit T2D. Protein rich diets decreased pro-inflammatory pathways depending on amino acids like glutamate. Symbiotic microorganisms in the gut are modulated by dietary compounds, minimizing and further eradicating the proliferation of pathogenic microbial population.

Keywords: Microbiota, Diabetes, Nutrition, Food microbiology, Human gut, Microbiome, Endocrinology, Glucose, Microorganisms, Intestinal microflora.

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Introduction

Diverse array of microorganisms found in the human intestinal system showcases complex interactions between microbes and the human gut in the cellular and molecular level. Exact etiology about the formation of microbes in the gut has been well established. The intestinal epithelial barrier is surrounded by mucus layers that surround MUC2 mucin, an inner dense and firmly adherent layer which prevents bacterial penetration and a looser outer layer where bacterial interaction occurs. Absence of MUC2 results in disruption of mucus layer organization, allowing bacterial contact with epithelium [1]. Signaling pathways between host and the microbial community have been established and contribute to inflammation which leads to diabetes. Nuclear Factor Kappa B (NFkB), Mitogen-activated protein kinase (MAPK), Peroxisome proliferator-activated receptor gamma (PPARy) and Activator protein 1 (AP-1) are some of the key modulating pathways that control microbial proliferation.

NFkB is a signaling pathway that regulates cytokines, enzymes, and growth factors, receptors including toll like receptors (TLRs) and lymphocytes such as T cells and B cells. NFkB is also involved in tissue cell interaction. MAPK signaling pathway regulates cell metabolism, cell morphology, cell cycle progression and gene expressions. PPARy signaling pathway is directly involved with certain human genes such as GLUT2 that precipitate its anti-diabetic response.

Type 2 Diabetes

Type 2 diabetes (T2D) is known as non-insulin dependent diabetes, where production of insulin may be normal or elevated, causing either a lack of glucose or an impenetrable absorption of glucose through the cell. The inconsistent uptake of glucose results in an imbalance of solute to solvent ratio, causing either very low or high glucose intake. Two main etiological factors of T2D are inflammation and insulin sensitivity. By decreasing or preventing these through anti- inflammatory cytokines and other aforementioned mechanisms, T2D can be prevented.

Genes that Affect Type 2 Diabetes

HLA II human genes have been mapped as one of the most prevalent family of genes that is correlative to the presence of diabetes. There are a vast number of studies on T1D and HLA genes, while T2D and HLA genes had limited studies. Nevertheless, multiple studies on HLA genes and T2D were present for Chinese, Finnish, Lebanese, Japanese and Swiss. In the Finnish study, HLA-Cw4 in T2D was investigated in 227 patients. 168 were treated with diet or oral antidiabetic and 54 were treated with insulin. HLA- Cw4 antigen was found in 38.7% of non- insulin dependent patients and 15.6% of the insulin dependent diabetic patients. Furthermore, increased frequency of HLA-Bw35 was detected in non-insulin dependent diabetic patients.

Insulin-dependent diabetic patients decreased HLA-B7, increased HLA-B8, HLA-B12 and HLA- B15. This data

provides sufficient evidence on the correlation of HLA genes and Type 2 diabetes [2].

Nutrition in the Diabetic Gut Microbiota

Food nutrition highly impacts human gut microbiota. According to clinical studies, humans from heterogeneous geographical locations, such as Europe, America or Asia, differ in their gut microbiota composition influenced by their food intake. In this review, diets and diet components in Type 2 diabetes gut microbiota will be closely examined.

Diet Components on T2D Gut Microbiota

The effects of probiotics on gut microbiota in T2D

Probiotics found in fermented dairies such as yogurt, cottage cheese, cream cheese, sour cream, crème fraiche, kefir or buttermilk highly correlates with the inihibition of diabetes. In a study on T2D patients, 300g/d of yogurt which contains *Lactobacillus acidophilus, Bifidobacterium lactis* for 6 weeks significantly decreased blood glucose, HbA1c ($p<0.05$), erythrocyte superoxide dismutase, glutathione peroxidase activities and total antioxidant status ($p<0.05$) compared with the control group. This evidently proves that probiotics inhibit diabetes inception [3]. Fermented cheese contains Mesophilic bacteria, *Streptococcus lactis* and *Lactococcus lacti*. Fermented milk like kefir contains Thermophilic bacteria. Other fermented dairy such as buttermilk contain *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, and *Bifidobacterium Bifidum*.

Decreased *Lactobacillus* and *Bifidobacteria* spp is caused by the NFkB mechanism. Specific strains found in probiotics such as *Lactobacillus reuteri* inhibit IL-6 upregulated by TNF-alpha through a study by Hsieh et al. on Sprague Dawley rats fed a high fructose diet for 14 weeks. *Lactobacillus reuteri* suppressed the expression of glucose, insulin, leptin, C-peptide, and lipid markers, indicative of its T2D prevention. It has also been implicated to reduce glucose and glycated haemoglobin in STZ induced diabetic rats study conducted by Lu et al.

Lactobacillus casei (LC) which is also found in probiotics decrease T2D. A study by Matsuzaki et al. on T2D-KK-ay mice reduced plasma glucose and modified immune response. Cytokine production, interferon-gamma and interleukin -2 which were inflammatory were inhibited upon oral administration of LC. Since inflammation is one of the main etiological factors of T2D progression, prevention effects of LC were warranted.

Lactobacillus rhamnosus was also treated in streptozotocin T2D rats. Study by Mihoko et al. lowered HbA1c, suppressed oxidative stress, and enhanced glucose tolerance and insulin secretion [4].

Lactobacillus acidophilus in STZ-induced diabetic rats improved diabetic dyslipidemia, inihibited lipid peroxidation and nitrite formation. It significantly lowered blood glucose and free fatty acids. Study by Yadav *et al*. fed high fructose diet to Wistar rats for 8 weeks. Dahi which is equivalent to yogurt inihibited the usual high progression of glucose, insulin and lipid profile levels triglycerol, cholesterol and blood free fatty acids [5].

Lactobacillus plantarum (LP) lowered plasma blood glucose levels in HFD fed mice by Andersson et al. Carboxylic acids were also detected between the control group and group fed with LP. Increased levels of acetic, propionic, butyric and other minor acids were observed upon administration of LP [6].

Bifidobacterium longum in HF reduced metabolic endotoxin concentrations and intestinal inflammation. It also increased expression of Reg I which regulated growth factors through a study conducted by Chen et al. [7].

Bifidobacterium animalis reversed bacterial translocation process and animals' inflammatory and metabolic status. This study led by Amar et al. fed fat-enriched diets for a week which proliferate commensal bacterial for those who expressed pattern recognition receptors Nod1 or CD14, except for Myd88 ob/ob mouse. Myd88 has been observed to reverse the inception of T2D and other HFD-induced metabolic diseases [8].

The effects of refined sugars and carbohydrates on gut microbiota in T2D

Conversely, foods such as refined sugars breed the overgrowth of opportunistic bacteria like *Clostridium difficile* and *Clostridium perfringens* by increasing bile output. *Clostridium perfringens* has been shown to strongly inhibit bile salt hydrolase (BSH), an enzyme mostly present in probiotics [9].

Absence of dietary nutrients underscores the reliance of certain gut derived bacteria to host glycans. One such is the *Bacteroides thetaoiotamicron* bacteria, which depend on glycans to survive. This circumstance supports the idea that endogenous carbohydrates influence gut microbiota.

Human milk oligosaccharides favor the growth of *Bifidobacteria* that lodge themselves in the mucin layer of the epithelial barrier. These *Bifidobacteria* stabilize tight junction formation in the Epithelium and induce anti-inflammatory cytokines such as IL-10, correlative of its inhibitory effects to T2D [10].

Bifidobacteria infantis has been implicated to secrete gut peptide through tight junction protein expression, reducing gut permeability barrier. Decreasing *Bifidobacteria infantis* strengthens the lipopolysaccharide membrane in mice according to a study by Cani et al. and inhibits pathogenic bacteria from entering the cell [11].

The effects of complex carbohydrates on gut microbiota in T2D

Whole Grains found in bread, pasta or rice is comprised of complex carbohydrates which also decrease susceptibility to T2D. Epidemiological studies show the inverse correlation between whole grain intake and C-reactive protein. As the etiology of T2D branch from inflammation and insulin sensitivity, the mechanisms of action should be targeted to eliminate these. Inflammation is caused by the abnormal aggregation of cytokines which inhibit insulin action in cells. As whole grains improve insulin sensitivity, it is able to combat the effects of inflammation [12]. Short Chain Fatty Acids decrease the presence of toxic bacteria that correlate with T2D. In a pioneering study by Louis et al. on mice, *Firmicutes* (*Eubacterium rectale* and *Blatia coccoides*), *Bifidobacteria* and *Bacteroides* were known to be upregulated through complex

carbohydrate intake producing short chain fatty acids that modulate T2D [13]. The mechanism behind this highlights the anti-inflammatory role of *Firmicute* strains such as *Eubacterium rectale and Blatia coccoides,* as well as other bacterial species such as *Bifidobacteria* and *Bacteroides*. In another study conducted, it showed that *Faecalibacterium prausnitzii* have anti-inflammatory effects that prevent the pathology of T2D [13]. I postulate then that these types of Bacteria enzymatically convert nutrient to SCFA such as butyrate that regulate inflammatory processes.

The effects of high fatty acids on gut microbiota in T2D

High omega-6 polyunsaturated fatty acids found in safflower oil, peanut oil, reduce *Bacteroidetes* species, increasing *Firmicutes*, *Actinobacteria* and *Proteobacteria* species [14]. In a study on 55 post-menopausal women with T2D, daily treatments of 8 g CLA and SAF were provided for 16 weeks. SAF decreased HbA1c and C-reactive protein. Conclusion established that 8 g daily of SAF improved glycemia, inflammation and blood lipids [15].

Conjugated Linoleic Acids (CLA) which belong to the polyunsaturated fatty acids have antidiabetogenic effects. CLA when interacted with gut microbes such as *Bifidobacterium breve* reduce proinflammatory cytokines such as Tumor Necrosis Factor-alpha, IL-1-beta, IL-6, IL-8 and increased antiinflammatory IL-10 that inhibit T2D. In this study by Wall et al., higher concentrations of eicosapentaenoic acids (EPA) and docosahexaenoic acid (DHA) were observed which were anti-inflammatory [16].

The effects of protein-rich diets on gut microbiota in T2D

Protein-rich diets increased the inception of bacterial enzymes such as b-glucuronidase, azoreductase, and nitroreductase. Proteins increase the proliferation of *Bacteroides* species according to a human study [17]. Metabolic strategies such as mass spectrometry, high performance liquid chromatography were utilized to extract metabolites and small compounds derived from the gut microbiome. One such biogenic amine, histamine, an amino acid, originated from *Lactobacillus reuteri* in the human gut. Histamine is produced from L- histidine by histidine decarboxylase inside this bacterium. Histamine suppresses pro-inflammatory signals, including TNF induced factors [18,19]. Furthermore, another amino acid which is implicated with T2D gut microbiota relates with the gamma butyric acid (GABA) from glutamate via glutamate decarboxylase and production of putrescine from ornithine. These amino acid metabolites prevent inflammation and decrease the inception of T2D.

Diets on T2D Gut Microbiota

The effects of vegetarian diets on gut microbiota in T2D

Vegetarian diets alter *Escherichia coli* and animal milk fat alpha proteobacteria. As shown in Table 1. Vegetarian diet consists of fiber that constitutes vegetables. Fiber, when digested, is characterized as a SCFA where the parallel metabolism of SCFA from whole grain exists. Through consumption of fiber, intestinal inflammation is inhibited. In a study by Kim MS et al. on six obese subjects with Type 2 Diabetes, strict vegetarian diets were assigned for one month. Strict Vegetarian Diet (SVD) reduced body weight, concentrations of triglycerides, total cholesterol, low density lipoprotein and haemoglobin A1c. SVD reduced the ratio of *Firmicutes*-to- *Bacteroidetes* in gut microbiota, and decreased pathobionts such as *Enterobacteriaceae*.

Increased microbes such as *Bacteroides fragilis* and *Clostridium* species were also expressed. This study underscored the importance of fiber in improving risk factors to metabolic diseases and shows that fiber consumption reduces gut inflammation by changing gut microbiota [20].

In a study by Uyeno et al. that tested the effects of vegetable kale on mice and their gut microbiota, ratio of *Firmicutes* to *Bacteroidetes* were observed to be higher for those fed with kale vegetable diet [21].

The effects of calorie restricted diets on gut microbiota in T2D

Calorie restricted diets have been known to attract *Clostridium coccoides, Lactobacillus* spp, and *Bifidobacteria* spp. Complex carbohydrates attract less *Mycobacterium avium* subspecies, *Paratuberculosis* and *Enterobacteriaceae*. In another study that tested energy restricted diets on obese subjects, *Bifidobacterium* was decreased [16].

Table 1. *Foods that alter microorganisms in the gut.*

Type of Food/Diet	Microorganism Upregulated or Downregulated to Prevent Diabetes
Refined Sugars	↑ *Clostridium difficile*, ↑ *Clostridium perfringens*
High Fat and Sugar	↑*Clostridium innocuum*, ↑ *Catenibacterium mitsuokai*, ↑*Enterococcus spp.*
Calorie Restricted	↑*Clostridium coccoides*, ↑*Lactobacillus spp*, ↑*Bifidobacteria spp*
Complex Carbohydrates	↓*Mycobacterium avium*, ↓*Paratuberculosis*, ↓*Enterobacteriaceae, Bacteroidetes*,↑*Bifidobacteria*, ↑*B. longum*, ↑*B. breve*, ↑*B. thetaiotaomicron*
High Omega-6 Polyunsaturated Fatty Acids	↓*Bacteroidetes*
Vegetarian Diets	↓*Escherichia Coli*
Animal Milk Fat	↓*Alpha proteobacteria*, ↑*Bifidobacteria*, ↑*Bacteroides prevotella*
Probiotics	↑*Lactobacillus (reuteri, rhamnosus, fermentus, plantarum)* ↑*Bacteroides (fragilis, thetaiotaomicron)* ↑*Bifidobacterium (adolescents, bifidum, breve, lactis)* ↑*Salmonella typhimurium, Streptococcus thermophilus Yersinia enterocolitica, Bacteroides vulgatus Enterococcus faecalis*

Study conducted by Zhang et al. observed that mice fed with low fat diet decreased strain of *Streptococcaceae* which were inflammatory. Furthermore, increased beneficial bacteria such as *Lactobacillus* was observed, preventing pathogen gut barrier adhesion and reducing inflammatory cytokines in which these mechanisms inhibit the inception of T2D [22].

The effects of high fat and sugar diets on gut microbiota in T2D

High fat diets have been discovered to reduce *Bifidobacterium* spp and *Bacteroides* related bacteria, *Lactobacillus* spp and *Roseburia* spp. *Firmicutes* increase while *Bacteroidetes* decrease [11]. In a study that utilized saturated fat from milk proteins, 8-Proteobacteria growth was triggered, specifically *Bilophila wadworthia* in the cecum [14]. Diets such as those rich in fat and sugar attract *Clostridium innocuum*, *Catenibacterium mitsuokai* and *Enterococcus* spp. In a study on healthy humans fed with high carbohydrate or fat meal, postprandrial endotoxenemia was induced, along with mononuclear cell expression of TLR4, SOCS, and NF-kB binding activity [16].

Surprisingly, a high fat, sugar rich diet characterized as "Western Diet" implicated as anti- inflammatory, according to a study by Backhed et al., where the diet constitute 41% fat, 41% sugar and 18% protein. The high fat and sugar rich diet elevated levels of Fiaf which induced Pgc-1alpha, and increased AMPK activity [23].

In a study by Cani et al., high fat diet reduced *Bifidobacterium* spp and *E. rectale/ Cl coccoides* which favored gram-negative to gram positive ratio. Moreover, lipopolysaccharides bind to CD14 and TLR4 which increase secretion of proinflammatory cytokines. This modulation of gut microflora significantly increased plasma lipopolysaccharide, fat mass, body weight, lipid triglycerides, diabetes and inflammatory tone. This study suggests the role of gut microbiota in modulating T2D [8].

Methods

Literature search

PubMed database was utilized to extract relevant papers from 1994 to 2012, with one from 1978 and another one from 1985. Keywords utilized were “microbiota”, “diabetes”, “nutrition”, “food microbiology”, “human gut”, “microbiome”, “endocrinology”, “glucose”, “microorganisms”, and “intestinal microflora”.

Study selection

Studies were restricted to Type 2 diabetes. Case-control, cohort, cross-sectional, randomized control trial, and meta-analyses. Studies were focused on nutrient interaction in the small and large intestines.

Subject

Mice and humans were utilized in experiments. Subjects from America, Asia and Europe were utilized.

Results and Discussion

From genes that affect type 2 diabetes to dietary components that modulate type 2 diabetes gut microbiota, it has been postulated that food microbiology, specifically probiotics, refined sugars, complex carbohydrates, fatty acids, protein-rich diets, vegetarian diets, calorie restricted diets, and high fat and sugar diets certainly modulate type 2 diabetics and their gut microbiota. For probiotics, it is generally confirmed that it decreased blood glucose thereby exhibiting its antidiabetic effects. Refined sugars, on the other hand, one mechanism induced an anti- inflammatory cytokine such as IL-10 which shows its inhibitory effects to type 2 diabetes.

Complex carbohydrates such as whole grains produce short chain fatty acids like butyrate that also regulate inflammatory processes, inhibiting the progression of type 2 diabetes. Fatty acids such as omega-6 polyunsaturated fatty acids reduced proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1-beta, interleukin-6, interleukin-8 and increased anti- inflammatory interleukin-10. This signifies the antidiabetic effects of good fatty acids. Protein- rich diets, such as those that contain histamine, an amino acid found in protein, suppressed tumor necrosis factor which is proinflammatory. This again underscores the antidiabetic effect of protein-rich diets. Vegetarian diets contain high antioxidants that increase insulin secretion, thereby contributing to its role in controlling and treating type 2 diabetes. It also contains fiber which releases short chain fatty acids, having a parallel mechanism for whole grains which also contain fiber. Calorie restricted diets decrease the strain of *Streptococcaceae* which were inflammatory. Therefore, calorie restricted diets will also control or treat type 2 diabetes. Finally, a high fat and sugar diet induces postprandial endotoxemia, which thereby increases its link with type 2 diabetes.

Conclusion

Examining human microbiota is critical to understanding the progression of diabetes. Food intake greatly influences human microbiota. Nutrition should be closely examined to establish prevention and treatment of Type 2 diabetes. Based on the literature present, it is of great evidence that the human microbiome tremendously affects the prevention and treatment of diabetes. Fraction of microorganisms such as *Lactobacillus, and Bifidobacteria* are beneficial to alleviating diabetes while remaining fraction of microorganisms such as *Clostridium difficile and Clostridium perfringens* increase the likelihood of obtaining diabetes. Through analyzing the studies involved in this review, importance of the intestinal microbiota and dietary consumption have been highlighted. Its relevance to the development of local and systemic immunity and colonic homeostasis must be considered crucially. Nutrition implicates an enormous role in modulating gut microbiota, transforming a balanced healthy microbiota. For instance, diets rich in complex carbohydrates such as pasta and bread prevent the growth of *Firmicutes* and *Bacteroides*. Complex carbohydrates increase levels of beneficial *Bifidobacterium* spp including *Bifidobacterium longum*, *Bifidobacterium breve* and *Bacteroides thetaiotaomicron*. Targeting Diet according to individual physiological function would merit a preventative method for Type 2 diabetes. Implications for future research suggest a more expansive intervention for examining microorganisms through biomarkers. Testing microbial content of human gut will

contribute to comprehending the diversity of microorganisms. Advancing the scientific literature and techniques in the prevention and treatment of the human gut microbiota would warrant a significant impact on the way we prevent and treat diabetes.

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