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Food Fortified with Carbohydrate-Fermenting Gut Microbes Producing Butyrate May Reverse Type 2 Diabetes Mellitus: A Silver Lining for Diabetes Research

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Abstract

Diabetes mellitus is a metabolic non-communicable disease affecting people of all ethnic groups around the world. To date, no cure for the disease is available except for its management by medication. It is a disease probably caused by changes in food habits, which alter the gut microbiome and certain bacterial species, their densities, and metabolic functions in the altered gut environment. Carbohydrate fermenting microbes producing butyrate may reverse Type-2 diabetes mellitus, as butyrate production in the gut environment regulates the blood glucose level and glucose intolerance. Species of *Faecalibacterium*, *Eubacterium*, *Clostridium*, *Ruminococcus*, and *Roseburia* are important carbohydrate-fermenting bacteria that are mostly involved in starch fermentation with the production of butyrate in the gut environment. Butyrates help to produce gut hormones that regulate blood sugar levels, which may improve insulin resistance. These bacterial species can be used to fortify the food material recommended for people with type 2 diabetes mellitus. A further research and formulation of such fortified food will be a silver lining for diabetes research. Available research suggests that certain foods, especially dry fruits and vegetables, are fortified with certain gut microbes, but not with the carbohydrate-fermenting butyrate-producing gut microbes, and therefore, it is of utmost importance for gut microbial diabetic research.

Keywords: Diabetes; Ethnic group; Gut microbiome; Butyrate; Fortified food

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic diseases in the world. Due to the rise in morbidity and mortality, it has become a global health problem. To date, T2DM still cannot be cured, and its intervention measures mainly focus on glucose control, as well as the prevention and treatment of related complications [1]. In type 2 diabetes, which affects approximately 463 million people worldwide, a person's body gradually loses its ability to regulate blood sugar [2] effectively. Although prior research has connected changes in the gut microbiome to type 2 diabetes [3,4], a diverse large-scale study at a global level has been lacking. Mai et al. [5] analyzed data from the newly established microbiome, and cardiometabolic disease consortium (Micro-Cardio), wherein the dataset included genomic information from the gut microbiomes of 8117 people who had type 2 diabetes, pre-diabetes, or normal blood glucose levels, and were ethnically and geographically diverse, hailing from the United States, Israel, Sweden, Finland, Denmark, Germany, France, and China. They found a consistent set of microbial species that were linked to type 2 diabetes across their study population, including many that had never been reported before. To understand the role of these microbes in the gut, the researchers analyzed the species functional abilities. They found that certain strains of microbes had functions that may be linked to varied type 2 diabetes risk. For example, a strain of *Prevotella copri*- a common gut microbe that has

the capacity to produce large quantities of branches-chain amino acids was more commonly seen in the gut microbiomes of people with type 2 diabetes. Previous studies have shown that people with chronically high levels of branched-chain amino acids in their blood have a higher risk of obesity and type 2 diabetes [6]. The researcher believed that changes in the gut microbiome cause type 2 diabetes.

Zhou et.al [1] reported that gut microbiota plays an important role in the development of metabolic diseases, especially T2DM [7] also opined that changes in gut microbiome may increase type 2 diabetes risk. It was found that specific species and strains of gut microbes were more common in people with type 2 diabetes. *Bacteroides* and *Bifidobacterium* are beneficial genera that are frequently reported in studies of type 2 diabetes. *Roseburia* and *Faecalibacterium* are found in lower frequencies in Type 2 Diabetes groups than in healthy control suggesting that their lower frequencies may be responsible for uncontrol metabolism associated with glucose regulation. According to a study by Candela et.al [8] type 2 diabetes patients had more Short-Chain-Fatty-Acid producers like *Faecalibacterium*, *Roseburia*, *Lachnospira*, *Bacteroides*, and *Akkermansia* in their gut microbiomes than the healthy individual who followed two different diet patterns (high fiber diet vs control diet). Zheng Li et al. [9] concluded that there is clear and growing evidence of a close relationship between the microbiota and diabetes, and this is worthy of future investments and research efforts. Dysbiosis in gut microbial composition and function is linked to immune responses and the development of metabolic diseases, including diabetes mellitus [9].

The composition of the gut microbiome may affect the likelihood of developing type 2 diabetes, according to the systematic review of Slouha et.al [10]. The changes to the microbiome may happen first, and diabetes develops later, not the other way around [5], and that prospective or interventional studies are needed to confirm this relationship. Research over the past decade has linked changes in the

gut microbiome to the development of type 2 diabetes but has not been able to draw significant conclusions because of those studies' small size and varied design. The gut microbiome's relationship to complex, chronic, heterogeneous diseases like type 2 diabetes is quite subtle. The microbiome is highly variable across different geographic locations, and racial and ethnic groups. The study of a small, homogeneous population will probably give inconclusive results. Therefore, large and diverse populations are necessary for detailed microbiome variation studies. If further research confirms that these changes indeed contribute to the development of type 2 diabetes, researchers could use that knowledge to try to manipulate the microbiome to reduce type 2 diabetes risk.

Research Needs

Gut microbiome studies (of diabetes and non-diabetes) of all the ethnic groups around the world

There are 26 Ethnic groups reported around the world [11]. People who have a common language, race, religion, or cultural background are considered to be an ethnic group. These are the area-specific people's groups, whose culinary and dietary practices differ from each other. It is apparent from Table 1 that irrespective of the variation in culinary and diet, the people from all these 26 Ethnic groups have diabetes. It means that it is not the diet that causes diabetes, but a change in diet and subsequent shift in the gut microbiome may be the reason for causing diabetes mellitus. Previous report from the metagenomics of the Human Intestinal Tract (MetaHIT) project indicated 32 core bacterial species in more than 80% of the European population that belonged to the genera *Faecalibacterium*, *Roseburia*, *Bacteroides*, *Dorea*, *Clostridium*, *Eubacterium*, *Coproccoccus*, *Ruminococcus*, *Alistipes*, *Collinella*, *Parabacteroides* and *Bifidobacterium* [40]. In this study, *Faecalibacterium*, *Eubacterium*, *Clostridium*, *Blautia*, *Ruminococcus* and *Roseburia* were found to be core gut bacterial genera across the representative population of the world [41] (both rural and urban).

Table 1: Ethnic groups, their geographical locations, food habits, and major non-communicable diseases for consideration of gut microbiome studies.

Ethnic Group ¹	Geographical Area	Food Habits	Major Non-communicable (MNC) Diseases
Aborigines	The native hunters and food gatherers of Australia	Traditional food habits include: Plant-based food high in dietary fiber and low in carbohydrates, especially starch. Fruits, Nuts, Seeds, Grains, and others. Protein source: Buffalo, moose, deer, duck, and fish. Diary was not traditionally consumed but was introduced by European settlers.	Diabetes, obesity, hypertension, and cardiovascular [12]
Afrikaners	White people in South Africa	Traditional Afrikaner food includes bredie (a meat stew), potjiekos (a slowly-cooked meat and vegetables stew), boerewors (spiced sausage), biltong (strips of dried meat), melktert (milk tart) and Koeksisters (sweet, plaited dough).	Hypertension, cardiovascular diseases, diabetes, cancer, mental illnesses, and chronic lung diseases like asthma [13]
Aleut	These people live between Alaska and Siberia on the Aleutian islands. They are related to Eskimos	The chief sources of food were whales, sea lions, seals and walruses, different types of fish and shellfish, wildfowl, and arctic birds.	Heart disease. Diabetes appeared lower (2 %of all deaths among Alaska natives) [14]

¹Source: Fact Monster 2024

Amish	A group of people in the rural U.S.	Amish cuisine is plain and rich in carbohydrates and lipids. They tend to have home gardens that provide fresh fruits and vegetables for seasonal consumption, as well as for canning, pickling, and storage during winter months. Their traditional cuisine focuses on wholesome, healthy, and delicious food often made with seasoning like thyme, cloves, and bay leaves as well as baking ingredients like sugar, butter, vanilla, and milk.	Cardiovascular disease, DM type 2., Cancer, tobacco and alcohol use, periodontal condition, traumatic injuries, fertility, and birthing [15]. Type 2 diabetes mellitus among Lancaster Amish is 50% lower than non-Amish [16]
Arabs	Arabs originated in the Arabian Peninsula. Some 150 million people in Africa and the Middle East	Arabs of the Arabian -peninsula relied heavily on a diet of dates, wheat, barley, rice, and meat with little variety and heavy emphasis on yogurt products, such as labneh (yogurt without butterfat)	Cardiovascular diseases, cancer, chronic lung diseases, and diabetes [17]
Armenian	The majority of the population of the Republic of Armenia.	Armenian food is based on olive oil and features a variety of ingredients that includes bread, butter, buttermilk, cheese, fresh and pickled vegetables and radishes, lamb, yogurt, eggplant, khorovats (kebab of Armenian fish) and Kyufta (minced meat, crushed wheat, and onions, rolled into a tapered shaped, vegetable or meatball soup with sour milk.	Cardiovascular disease, cancer, diabetes, chronic respiratory diseases. Other risk factors for NCD include tobacco use, harmful alcohol use, unhealthy diet, and physical inactivity [18]
Barbarians	Barbarians were known to the Romans as anyone living outside the Roman Empire, AD. 400-1000.	They consume more meat than grains and know little of good dining etiquette.	Ischemic heart disease, lower respiratory infection, stroke, low back pain, major depressive disorder, preterm birth complications, congenital anomalies, diabetes [19]
Basques	Lives in the Pyrenees mountains, between Spain and France. Their language is unrelated to any other in the world	Pintxos, Marmitako (fish stew), grilled meats and fish, rich cheeses, and drinks Txakoli. Olive oil is more commonly used than vegetable oil in Basque cooking. Potatoes and capsicum, are used in hams, and sausages.	Ischaemic heart disease, type 2 diabetes, and colorectal cancer [20]
Bedouins	They are nomads in the Arabian Desert.	Bedouin tribe's food habits are centered around the animals they herd and include meat (of sheep, goat, and camel), halleb (milk), cheese, samen sheehi (herb ghee or butter from the milk), khubz (wheat bread cooked on a hot stone), vegetables and fruit, Freekeh (made from immature wheat and barley) and lentils.	Cardiovascular and diabetes [21]
Bushmen	A primitive nomadic people who live on the edges of the Kalahari desert in Namibia, Botswana, and South Africa. The average bushman is just over 4 feet tall.	They are hunter-gatherers, hunting with bows and arrows, trapping small animals, and eating edible roots and berries They eat a variety of foods including meat, corn, wild plants, and vegetables. They cook their food on the open fire.	Cardiovascular disease, diabetes, Cancer, Chronic respiratory diseases, and mental illness and disorders [22].
Cajun	Cajuns settled in Louisiana, far from their original home in Nova Scotia, Canada. Their style of cooking remains distinctive	Although there is a large variety of dishes, rural Cajuns generally prefer dark roast coffee, highly seasoned foods, hot peppers, vegetables smothered in brown gravy, and one-pot dishes served with rice. Their dishes are referred to as Gumbo, Jambalaya, cornbread, beignets, Pain perdu, and Alligator.	Cardiovascular diseases, Cancer, Chronic respiratory diseases, Diabetes, Hypertension, Periodontal disease, Osteoarthritis, Ischemic heart disease, Osteoporosis, COPD, Asthma, Mood and anxiety disorder [23]
Celts	The Celts date from the Iron Age, and their descendants are spread throughout Ireland, Scotland, Wales, Brittany, Cornwall, and the Isle of Man, their common Celtic language, such as Gaelic in Ireland, makes them an ethnic group.	The diet varied and included grains, root vegetables, wild food, meat, dairy, and honey.	Cardiovascular diseases, Cancers, Chronic respiratory diseases, and diabetes [24]
Creoles	People born on the island of the West Indies to European parents, people born in the U.S. Gulf states to French or Spanish parents, and people of mixed French or Spanish and African-American descent.	Creole cuisine includes Gumbo (a stew made with a variety of meats, vegetables, and roux-based sauce. A base diet of coconut milk/oil, rice, beans, chicken, fish, and other game meats.	Cardiovascular diseases, cancer, and diabetes [25]
Dravidian	The largest Dravidian ethnic groups are the Tamils from Tamil Nadu, Sri Lanka, and Malaysia, and the Telugus from Andhra Pradesh and Telangana.	The food of Dravidian tribes varies depending on the tribe and their habitat, but often includes forest products, meat, and tubers. Some food habits of Dravidian people include rice, appalam, vadai, and Tayir vadai. Rice is a major staple food.	Diabetes, high blood pressure, cardiovascular diseases, and cancer [26]. Other NCDs include chronic respiratory diseases and mental disorders.

Gypsies	Originally from India, these monadic people are found in various parts of Asia, Europe, and North America. They speak the language of Romany. Some 400,000 Gypsies live in the U.S. today.	The food of Gypsies includes spices, stews, bread, coffee, pirogo, szaloncukor, fried bread dishes, hedgehogs, chicken, potatoes, pasta, rice and dumplings, fruits and vegetables, and sweet drink.	Type 2 diabetes, metabolic syndrome, and cardiovascular diseases [27]
Inuits	Eskimo is the European name for Inuits, who live on the coasts in the Northern parts of North America and Siberia.	Inuit traditionally ate a diet based on hunting and fishing. This includes moose, caribou, elk, seal, whale, buffalo, rabbit, all kinds of fish, and many species of bird. Every part of an animal is consumed or used to make clothing or shelter. Edible plants include corn, squash, fiddleheads, wild rice, nuts, and wild berries.	Inuit had a higher prevalence of heart attack, stroke, diabetes, obesity, and hypertension [28].
Kurds	Their homeland is Kurdistan, and extends through Iran, Syria, and Turkey. They live by farming.	Kurdish cuisine based largely on meat and rice, also incorporates a diverse array of herbs, vegetables, and spices. It contains fresh naan bread and salad, seasonal fruits, local fish, and a hot cup of black tea, with lots of sugar.	Hypertension, musculoskeletal conditions, diabetes, and cardiovascular disease [29]
Lapps	They are nomadic people who used to follow the reindeer herds of northern Scandinavia and are known for their colorful clothing. Their territory is called Sennoscundia.	The food includes the meat of reindeer, breed cheese, fish, mushroom, barley flatbread, almonds, and potatoes. It is packed full of fresh flavors such as fresh berries, mushrooms, and game.	Cardiovascular diseases, Cancer, Respiratory diseases, Diabetes [30]. Other NCDs are Dementia, Osteoporosis, and fractures.
Mestizos	Mestizos are Latin American people who are usually a mixture of European and Native American descent.	The culinary dishes included Bandeja Paisa (that combines beef, pork sausage, rice, avocado, Andean beans, corn patties, and grilled plantain); Banana-leaf tamal (made up of small cuts of meat in a rice flour mix, wrapped in banana leaves and boiled); Garnaches (fried corn tortilla with refried beans and shredded cheese); Tamales (made from ground corn and chicken, wrapped in banana leaves and steamed).	Cardiovascular disease, Cancer, Diabetes, and chronic respiratory disease [31]
Mongols	An East Asian ethnic group native to Mongolia, China, Buryatia, and Kalmykia republics of Russia.	Mongolian people prefer to eat lamb as their staple food rather than rice. Wheat, barley, and buckwheat predominate more than rice in modern Mongolia. Their diet includes dairy products, meat, fruit, vegetables, wild game, bread, and Airag (a fermented mare's milk).	Cardiovascular disease, and Cancer [32]. Other NCDs include diabetes, stroke, and chronic lung disease.
Tribal people	A tribe is a group of families with a common way of life. Tribes resist cultural change, preferring to keep their own traditions.	Tribal communities often eat foods that are naturally available in their environment, such as fruit, millets, tuberous plants, and seasonal vegetables. Their diets may also include wild catches, fish, and insects, and they commonly use traditional preparation methods like fermentation and smoking.	Cardiovascular disease, Cancer, Chronic respiratory disease, hypertension, and Diabetes [33]. Other NCDs are stroke, epilepsy, and sickle cell disease.
Maoris	The first inhabitants of New Zealand. They may have travelled there by canoe from Polynesia. They are tall, broad-faced, brown-eyed people who speak the Maori language. Maoris greet each other by pressing their noses together.	The traditional diet was based on fish, birds, wild roots and herbs, and root crops brought from Polynesia. Their traditional form of cooking was in earth ovens. Their traditional food habits include Hangi (cooking in an underground pit oven), and Rewena bread (Maori bread that uses a fermented potato starter called rewena).	Cancer, Ischemic heart disease, Chronic lower respiratory disease, Diabetes, Asthma, Rheumatic heart disease, and chronic pulmonary disease [34].
Maasai	Maasai are East African nomads who live by herding sheep and cattle. The tall and slender Maasai live in mud houses.	Maasai have a traditional diet that centers around cattle and includes milk, meat, blood (blood from cattle obtained by nicking the jugular vein. Mixed blood and milk is a ritual drink), honey, fruits, and herbs. Maasai have added farm crops such as maize meal, rice, and cabbage to their diet. Masai also uses plants to make boiled soups.	Cardiovascular disease, chronic respiratory disease, cancer, and diabetes [35]. Other NCDs include sickle cell disease, mental disorder, eye and ear disorder, hypertension, Alzheimer's, and Osteoporosis.
Pacific Islanders	Original people of Oceania's three major subregions (Melanesia, Micronesia, and Polynesia) or any other island in the Pacific Ocean.	The traditional diet included a variety of food such as root- crops (like taro, yams, breadfruit, cassava, sweet potato, banana, plantain, pandanus, and arrowroot); coconut, green leaves, fruits, fish and sea food	Cardiovascular disease, chronic respiratory disease, cancer, and diabetes [36].

Pygmies	The Pygmy tribe of the D.R. Congo, Africa is a peaceful, nomadic group that hunts and gathers its food. Pygmy's skin is a light yellow-brown. Adult male Pygmies are less than 5 feet tall. Pygmy tribes also live in the rainforests of India and the Philippines	Pygmy tribes are partially hunter-gatherers and their diet consists of wild meat and gathered plant foods, wild food, and honey.	Cardiovascular disease, chronic respiratory disease, cancer, and diabetes [37].
Watusi	People who raise cattle in Burundi, Africa. They are among the tallest people in the world. Many of the adult males are more than 7 feet tall.	Their food habits include Milk and dairy, meat, banana, and sorghum beer, and grown crop food. Milk and salted butter are their staple food.	Cardiovascular disease, chronic respiratory disease, cancer, and diabetes [38,39].

Further study of the gut microbiome may need to assess the presence of gram-negative bacteria [30] in these ethnic groups with diabetes and non-diabetes. Gram-negative bacteria may produce gut microbial variables such as bacterial Lipopolysaccharides (LPS) [42]. LPS is a toxin that induces insulin resistance, Type 2 diabetes, and Alzheimer's disease. Plasma LPS may need to be measured in these ethnic groups to reduce the risk of Type 2 diabetes.

The bacterial species, particularly *Faecalibacterium*, *Eubacterium*, *Clostridium*, *Ruminococcus*, and *Roseburia* are important carbohydrate-fermenting bacteria that are mostly involved in starch fermentation with the production of butyrate. Butyrate is a Short-Chain Fatty Acid (SCFA) produced by gut microbiota that plays a key role in gut health with various functions. Butyrate is the primary energy source for colonocytes. It strengthens the gut barrier by targeting tight junctions, the mucus layer, and the production of antimicrobial peptides. It inhibits inflammation and oxidative stress. It can protect against epithelial injury and improve tissue repair. It promotes a healthy microbiome. It regulates metabolism and helps with the transepithelial transport of fluids. It helps to prevent non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, inflammation, cancer, and liver injuries. Butyrates help to produce gut hormones that regulate blood sugar levels, which may improve insulin resistance and obesity. Butyrate is produced from fermentative carbohydrates of plant-origin food material, such as fibers, cellulose, and complex sugar in the colon with the help of gut bacteria [43]. Therefore, the production of butyrate in the gut by the gut microbiome seems to be the most important aspect in the regulation of blood sugar levels and needs further confirmation.

It will be advisable to study the gut microbiome of all the ethnic groups (diabetes and non-diabetes) to assess the presence/absence of carbohydrate-fermenting gut bacteria with their population density variation among diabetes and non-diabetes. This will give a clear-cut picture of gut microbial variables in these people. Once it is confirmed that carbohydrate fermenting bacteria and butyrate produced by these have a role in the regulation of blood sugar and diabetes, these can be used in the form of probiotics in the management and probably reversal of diabetes mellitus all over the world.

Furthermore, the performance of probiotic bacterial strains is influenced by the carrier food and its functional components, which while buffering the probiotic through the gastrointestinal

tract, contribute to an efficient implantation of bacterial cells and regulate probiotic features [44]. Plant-based matrices are eligible substrates for hosting and delivering microbial populations because of their richness in nutrients, fibers, vitamins, minerals, and dietary bioactive phytochemicals. The health-promoting properties of solid plant-based matrices (particularly artichokes, table olives, apples, and cabbage) and their association with probiotic bacteria are indicative of the role of the food matrix in sustaining probiotic cells during product processing, digestive process, gut implantation, and finally in exerting beneficial effects [2,3]. The functional attributes of plant-based matrices, their structure and their suitability to fermentation make them appropriate for carrying probiotic strains that would take advantage of the characteristics of plant-based matrices and, by exploiting prebiotic and bioactive molecules, take benefit for their survival during product processing and shelf life as well as in the digestive process and gut colonization [45]. The available research on fortified food items with probiotics suggests that carbohydrate-fermenting probiotics producing butyrate can also be used in food fortification and diabetic reversal programs [46].

Conclusion

Diabetes mellitus, widely prevalent around the world in people of all ethnic groups, is probably caused by a change in carbohydrate metabolism, as a result of various factors, including changes in food habits. This change in food habits alters the human gut microflora responsible for carbohydrate metabolism. The involvement of certain gut microbial species related to carbohydrate metabolism plays an important role in the disease initiation and prevalence. These bacterial species, as probiotics, can alter carbohydrate metabolism and thereby diabetes. The food fortified with these carbohydrate-fermenting, butyrate-producing bacteria can be of significant importance in reversing type 2 diabetes.

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