Can modification of the gut microbiome with diet affect the onset and pathogenesis of diabetes

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Introduction

The human microbiome, especially the gut microbiome, has a role in protecting the body from harmful bacteria. The gastrointestinal tract harbours a complex and diverse microbiota that has an important role in host metabolism. Microbial diversity is influenced by a combination of environmental and host genetic factors and is associated with several polygenic diseases.

Diabetes is characterised by abnormal fuel metabolism, hyperglycaemia and dyslipidaemia, due to defects in insulin secretion, insulin action, or both. Type 1 and type 2 diabetes are characterised by low levels of high density lipoproteins (HDL) and high triglycerides rich particles, such as very low density lipoprotein(VLDL), as well as small LDL particles. In contrast to type 1 diabetes, the dyslipidaemia of type 2 diabetes is due to insulin resistance (which leads to increased hepatic production of VLDL).

Dietary interventions that modify the gut bacteria can have a positive role to play in those who have a predisposition to diabetes and those already suffering from diabetes whether type 1 or type 2. A significantly large number of publications have advocated the importance of diet in the onset and pathogenesis of non-communicable diseases like diabetes.[1] The diet recommended should be low in saturated fat and refined sugar but high in complex carbohydrate and whole grain, with a good measure of fermented products. Processed food or 'fast food' is responsible for the onset and progress of type 2 diabetes, but little scientific data has been presented to support this.[2] With the development of the Human Microbiome Project (HMP) and subsequent categorisation of the metagenome, we are at a stage where we can specifically say which diet causes an increase of what type of bacteria in the gut. By using biomarkers such as 16S rDNA to predict the onset of diseases using gut microbes, we have further strengthened the age-old view that diet modification can and will change the onset and pathogenesis of diabetes. The gut microbiome change acts by modifying the molecular signalling pathway and affects the metabolic status of the individual.

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Worldwide occurrence of diabetes

It is estimated that the global average prevalence of diabetes is around 10%, with 6% of all death in Africa[3] being due to diabetes. Dr Margaret Chan, Director-General of the World Health Organization (WHO) said, 'one in ten adults has diabetes worldwide, non-communicable diseases currently cause almost two-thirds of all deaths worldwide.' Every 10 seconds a person dies from diabetes.[5] Mauritius ranks third in the world as far as the prevalence of diabetes is concerned. One out of two Mauritians is either diabetic or has already reached the pre-diabetic stage.[4] Mauritius has a prevalence rate of type 2 diabetes of 19.3%, which might increase to 98% by 2030.[5] WHO called upon countries to strengthen the National Non-Communicable Diseases Programme within the framework of the Global and Regional Strategies on Prevention and Control of NCDs. The World Diabetes Day theme for 2012 was 'Protect our Future'.[6]

The human microbiome

The initial Human Microbiome Project (HMP) provided an unprecedented resource to detect, catalogue, and analyse relationships of human microbes. The human body is a complex ecosystem where microbes compete and cooperate. These interactions can support health or promote disease.[7] Most relationships of microbes are strongly niche-specific, with only a few hub microorganisms forming links across multiple body areas. Phylogenetic distance has a strong impact on the interaction type: closely related microorganisms co-occur within the same niche, whereas most exclusive relationships occurr between more distantly related microorganisms. These interactions are also widespread in microbial communities, where microbes can exchange or compete for nutrients, signaling molecules, or immune evasion mechanisms. These interactions among human-associated microbes may influence host health or disease.[8] In nature, organisms rarely live in isolation, but instead coexist in complex ecologies with various symbiotic relationships. As defined in macroecology, observed relationships between organisms span a wide range including win-win (mutualism), win-zero (commensalism), win-lose (parasitism, predation), zero-lose (amensalism), and

lose-lose (competition) situations.[9] Individual microbial interactions are essential for community stability in the healthy commensal microbiota. Characterising the key microbial interactions within the human body serves as an important first step for studying and understanding transitions among various healthy microbial states and disease-linked imbalances. Key taxa include members of the *Firmicutes*, which act as network hubs coordinating many relationships throughout the microbiome.[9] The ratio of *Firmicutes* to *Bacteroidetes* evolves during different life stages. Thus, for infants, adults, and elderly individuals, measured ratios are 0.4, 10.9, and 0.6 respectively[1,9].

Why focus on the microbiome?

Humans have coevolved with a vast number of microbes that live within and upon us. Our microbiota is more like an organ than an accessory. These microbes are key contributors to human health and several human ailments have been closely linked to the composition of the gut microbial community.

Like a polymorphism in the human genome, a change in the human microbiome can lead to a new phenotype that causes a disease or contributes to its progression. Some individuals are more susceptible to diseases while others are impervious. Unlike the human genome, the microbiome is a 'flow reactor' of genes. Its composition is dynamic; control over the content and architecture of our microbial communities can harness a new category of therapeutics that target the microbiota and modulate microbe–microbe and microbe-host interactions.[10] Gut dysbiota causes gut microbiota to enhance the extraction of energy from diet and regulate whole-body metabolism towards increased fatty acids uptake from adipose tissue, and to shift lipids metabolism from oxidation to *de novo* production. Obesity and high-fat diets relate to a specific gut microbiota, enriched by *Firmicutes* and with less *Bacterioidetes*.[11]

Microorganisms in the gut

The gut microflora has many useful functions, such as fermenting unused energy substrates, training the immune system, preventing the growth of harmful pathogenic bacteria, regulating gut development, producing vitamins such as biotin and vitamin K, and producing hormones to direct the host to store fats. Most bacteria belong to the genera *Bacteroides*, *Clostridium*, *Fusobacterium*, *Ruminococcus* and *Bifidobacterium* and to a lesser extent *Escherichia* and *Lactobacillus*. Also, fungi such as *Candida*, *Saccharomyces*, *Aspergillus*, and *Penicillium* have a mutualistic relationship.[12] Analysis of adult intestinal microbiota showed four bacterial divisions: *Firmicutes* (64%), *Bacteroides* (23%), *Proteobacteria* (8%), and *Actinobacteria* (3%); whereas in the infant microbiota there is *Staphylococcus*, *Streptococcus*, *Bifidobacterium*, and *Enterobacteria*.[13] Age, genetics, and diet are three important factors that trigger changes in the composition of these genera.[14]

Modification of the gut microbiome by dietary modification

A high-fat diet decreases *Bifidobacteria* which is important in maintaining the gut barrier. High n-6 PUFA, available in safflower oil, decreases *Bacteroidetes* and increases *Firmicutes*, *Actinobacteria* and *Proteobacteria*. Complex carbohydrates increase *Bacillus longus*, *B breve*, and *B thetaiotamicron*; whereas carbohydrate-reduced diets increase *Bacteroides*. Calorie-restricted diets decrease *Lactobacillus* spp and *Bifidabacteria*. High-sugar diets (especially refined sugar) increase *C innocuum*, *C difficle* and *C perifringes*.[14] In persons suffering from type 2 diabetes, the *Bacteriodetes/Firmicutes* ratio increases.[15] In obese individuals there are less *Bacteriodetes* and more *Enterobacteriaceae* and less *Bifidobacteria*.[15,16] Diet plays a key role in the composition of the gut microbiota which can be modified by modifying molecular signalling.

Molecular signalling and its effect

The microbiome can transfer metabolic disease by mechanisms which involve modulation of energy harvesting capacity, low grade inflammation, and corresponding immune responses on adipose tissue plasticity, hepatic steatosis, insulin resistance and secondary cardiovascular events.[17]

The interaction of intestinal epithelial cells with microbes and components released by them can allow bacterial fragments to diffuse through the mucosa to bind to epithelial cell receptors. *Bifidobacterium* is important in maintaining the gut barrier. Lower levels of *Bifidobacterium* lead to increased gut permeability, allowing Lipopolysaccharide (LPS) to get into the bloodstream. The immune system recognises LPS as a toxin and can cause inflammation and insulin resistance. LPS triggers systemic inflammation, increase in weight gain, increased insulin resistance, and increased macrophage accumulation in white adipose tissue. Processed food and high-fat diets augment this translocation of LPS.[18,19] Glucagon, such as peptide 1 (GLP-1) secreted by intestinal L cells is a potent antiglycaemic hormone, it also restores the glucose sensitivity of pancreatic beta cells, with mechanisms involving increased expression of GLUT-II and glucokinase. Glucagon inhibits beta cell apotosis, and stimulates proliferation and differentiation of beta cell inflammation and alters gut microbiota by modulating GLP-1.[20] Toll-like receptor-2 (TLR-2) plays an important role in pathogen recognition and innate immunity, which can lead to obesity, glucose intolerance, and insulin resistance. Persons having defective TLR-2 have a higher proportion of *Firmicutes* and a reduction of *Bifidobacterium* in their gut microbiome.[21-22] MyD88 is a protein which is a key regulator of immune responses to resident microbes and lack of it altered the microbial species in the gut. [23]

Dysbiosis, altered gut metagenome, and subsequent altered metabolic activities, in combination with classic

genetic and environmental factors, may promote the development of metabolic disorders.[24]

The way forward

Pharmabiotics is any form of therapeutic exploitation of the commensal flora, including the use of live probiotic bacteria, probiotic-derived biologically active metabolites, prebiotics, synbiotics, or genetically commensal bacteria. Probiotics are defined as live microbes that confer a health benefit when consumed in adequate quantities. *Bifidobaterium* and *Lactobacillus* are prominent probiotics.[23,25] Strains of the two dominant intestinal phyla, *Bacteroidetes* and *Firmicute*s, may prove more effective as probiotics in conferring health benefits than the currently popular *Lactobacillus* species. In the future, probiotics (like biologics and small-molecule drugs today) may be developed by pharmaceutical and biotechnology companies, approved by the Food and Drug Administration (FDA), and prescribed by physicians.[26]

Prebiotics are compounds administered to a microbial community to selectively stimulate growth of a specific subset of microbes. Enrichment of a specific prebiotic polysaccharide in one's diet may permit preferential expansion of a microbial group that is well adapted to its use. Prebiotics have considerable therapeutic potential and may benefit from the co-administration of probiotics.[25,26]

Microbiome engineers will eventually be able to use microbial cells as a new platform to modulate human biology, including decreasing susceptibility to pathogens, improving the efficacy of oral vaccination campaigns, and altering the trajectory of autoimmune conditions. Similarly, the gut microbiota may be a unique lever by which host energy balance can be tuned, either by exerting a direct influence on host metabolism, or by changing the efficiency of microbiota-facilitated caloric harvest from the diet.[15,26]

Discussion

In diabetes there is an imbalance of two dominant group of bacteria *Bacteriodetes* and *Firmicutes*, which in turn generates signals that control expression of genes by epithelial intestinal cells.[25] In 2009, Mai and Dragonov from Florida, USA suggested that pre- and probiotic products could modify microbiota composition, and be used effectively to control obesity and diabetes.[23] In 2010, Wu et al, from China, using molecular analysis of fecal microbiota, showed that *Bacteroides vulgates* and *Bifidobacterium* genes were low in a diabetic group.[22] Round et al, observed that microbiota impact on the immune response of the host.[26] Valladares et al, showed *Lactobacillus johnsonii* and *L reuter* isolated from biobreeding rats inhibits the onset of type 1 diabetes in diabetes-prone rats.[21] Giongo et al, from the USA, observed that *Bacteroides ovatus* increased in type 1 diabetes.[27] Toddlers destined to develop type 1 diabetes develop a microbiome that is less diverse and stable.[27] Musso *et al* from Italy said that Western diet had a role in promoting obesogenic gut microbiota.[28] Hattori and Taylor believe that human intestinal microbes open a new frontier for the assessment of risk for diabetes.[29]

Conclusion

Future research needs to unravel the hormonal, immune-modulatory, and metabolic mechanism underlying the microbe–microbe and microbe–host interaction. The modulation of this could be achieved by a drug designed specifically for individual gut microbiomes to combat metabolic disorders. This could increase therapeutic efficacy by giving personalised healthcare, where the therapeutic approach could be on the cause rather than the consequence. Therapeutic changes in microbiomes can be brought about by consuming fermented food such as salsa, sourdough bread, honey wine, 'kim chi' (a Korean pickled dish), miso (a Japanese fermented soybean), barley, brown rice, or other grains with the fungus *Aspergillus oryzae*, and tempeh produced by the fungus *Rhizopus oligosporus* added to partially cooked soybeans. Dietary benefits can occur with consumption of yoghurt which has four major strains of bacteria *L acidophilus*, *L bulgaricus, S thermophilus, and Bifidobacteria*.[30] Dietary supplementation of fermented papaya preparation reduces the oxidative stress of diabetes as found by researchers in Mauritius.[31] Heavy processing of food, frequency of treatment with antibiotics, and advances in hygiene in advanced countries have reduced the stability of the gut microbiome. A rigorous dietary and lifestyle change can go a long way towards altering the gut microbiome and helping to curb the modern scourge of diabetes.

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