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Review Article

GUT MICROBIOTA AND DIABETES MELLITUS - AN INTERLINKAGE

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ABSTRACT

In recent years, the curiosity to investigate the relationship between gut microbiota and diabetes development has increased. Evidence from previous studies suggests that gut microbiota manipulation may assure to prevent diabetes development in future, primarily in susceptible individuals. Here, we reviewed special gut microbiota types proposing development of Type 1 (T1D) and Type 2 diabetes (T2D) in humans and laboratory animals. The available data we found are still inconclusive and required more attention in discriminating specific groups of gut microbiomes strongly indicating T1D and T2D development or prevention. Further, we suggested for the first time to study the gut microbiota in different ways to find the root cause of diabetes development.

Keywords: Type 1 diabetes, Type 2 diabetes, Microbiome, Microbiota, Symbiont, Probiotics, Prebiotics, Complications.

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INTRODUCTION

Diabetes mellitus (DM) has become a health burden to many nations affecting both aging and young population. It is pertinent to analyze and realize the causes and mechanism of DM to plan a strategy for its prevention, management, and treatment.

Humans gut have intricate gathering of microorganisms. These days, gut microbes analysis in diabetic population has increased attention of many researchers to identify the relationship between certain type of gut microbe and DM pathogenesis. Altered gut microbiota in rodents and humans have suggested as an etiology to develop Type 1 diabetes (T1D), Type 2 diabetes (T2D), and obesity [1-3]. Similarly, a promising approach using antibacterial drugs, probiotics, and prebiotics further shown intestinal flora modification in obese and diabetes subject that affected body weight, insulin sensitivity, and metabolism [4]. A promising evidence from previous studies using animal model has strongly indicated T1D and T2D development due to gut dysbiosis and approach to manipulate this microbial community may help to prevent T1D in susceptible family individuals [5]. The dietary and environmental factors may also induce genetically susceptible individuals to develop diabetes, but data are supporting this hypothesis are still inadequate.

REASON I- UNFRIENDLY GUT MICROBIOTA TRIGGER T1D THROUGH INFLAMMATION AND AUTOIMMUNITY

It is believed that altered gut microbiota plays a crucial role in gut immunity and autoimmunity of pancreas [6]. In this aspect, it is understood that the gut microbiota has become a target in the prevention of T1D. Antibiotics and similar compounds may inhibit friendly commensals and alternatively may also favor to colonize with microbes that lead to beta cell autoimmunity and T1D by altering flora, permeability and immune mechanism directly or indirectly in gut [6]. Beside habits of taking a huge amount of antibiotics, high-calorie diet scan also grow obesogenic and diabetogenic type of microbes in patients that lead to obesity, insulin resistance, and diabetes by excessive energy harvesting from diets and depositing to liver and adipose tissue; modulating peptides secretion and receptors shape and intestinal barrier integrity [4]. This is experimentally proved using animal models. Similar study is required in human model time to time to know if the gut is being colonized with altered flora. Otherwise, this will put highest threats to patients and also challenges clinician to plan a strategy to monitor the situation in qualitative and affordable manner. In this regard, use of prebiotics and probiotics has also assured with promising outcomes [7].

Using molecular and metagenomics techniques, the role of gut microbial species in obesity and diabetes development elucidated elevation in nutrient absorption, intestinal transit time, *de novo* lipogenesis, and cellular storage; further lowering fatty acid oxidation, altering intestinal barrier, enterohepatic cycle and polyunsaturated fatty acid in tissues due to endotoxin-mediated chronic inflammation [8]. These changes were suggested due to the disappointing factors that are capable of inducing or triggering innate and mucosal immunity, further inviting autoimmune response to produce Type I diabetes [9].

This immune response also damages pancreas through beta cells destruction by lymphocytes that may have similar receptors for either of *Bacteroides*, butyrate-producing bacteria, *Enterovirus,* and cow milk antigen [10]. This kind of pathogenic immune response may be stopped by manipulating the gut microbial community to prevent islet destruction in pancreas [11].

Further, this was proved using probiotics in animal and human helped to reduce inflammatory autoimmune response, permeability and oxidative stress in gut; enhanced insulin sensitivity and adhesion proteins production in gut [11,12].

The available data from human and mice model study gave the evidence of developing obesity, T2D ad Alzheimer's disease due to the involvement of few gut microbiota in the pathogenesis [13]. The inflammation inducing factors produced by altered gut microbiota increases the risk of developing T2D. These microbiota should be identified for early diagnosis, approaching new therapeutic agents and developing novel drugs [14].

It is further clarified that diet and age alter gut microbiota. Lipopolysaccharides derived from bacterial membrane, short chain fatty acids (SCFAs) derived from fermentation of dietary fibers and products obtained from bacterial modulation of bile acids act as signaling molecule in host [15]. These molecules increase intestinal permeability which further increases absorption of macromolecules from intestine. The absorbed molecules induce immune response,

inflammation and alter signaling pathway in the host that affect glucose and lipid metabolism triggering the development of T2D [15].

SCFA produced by gut microbiota affect the production of cathelicidin-related antimicrobial peptide (CRAMP) by beta cells that are linked with the incidence of autoimmune diabetes. CRAMP is associated with the normal immune functions in pancreas. Modulation in CRAMP production leads to inflammation of pancreatic islets and development of autoimmune diabetes. This was observed clearly in an animal model [16].

Similar research suggested pro-inflammatory cytokines such as monocyte chemoattractant protein-1 and interferon gamma production in response to cell wall lipopolysaccharides which causes low-grade chronic inflammation in human gut. Enzyme-linked immunosorbent assay shown significant elevation of these inflammatory cytokines in T2D patient in compare to non-diabetic subjects. Metagenomic analysis in a stool sample of T2D shown predominance of Gram-negative bacteria mainly *Escherichia* and *Prevotella* whereas non-diabetic patient shown predominance of Gram-positive organisms mainly *Faecalibacterium*, *Eubacterium*, and *Bifidobacterium* [17].

Along with evidence especially in developed country suggested the development of T1D due to the direct involvement of gut microbiota in immune-mediated pathogenesis [18]. Research studies have proven the role of altered gut microbes in the immunopathogenesis of DM; on the other hand, probiotics which have beneficial role in making healthy gut, have been suggested in DM management [19].

It has been introduced that T1D and T2D develop due to possibility of changes in gut microbiota type and population that causes an adverse effect on gut immunity, bowel function, digestion rate, energy storage, systemic inflammation and insulin resistance, and impairment. In view of these possibility treatments strategy has been suggested with fecal transplantation, prebiotics and probiotics formulation and recommendation [20]. Intake of prebiotics in the form of non-digestible carbohydrates had been suggested to improve intestinal permeability and inflammation conditions generally induced by altered gut microbiota that further develop diabetes. This study was verified in children with T1D [20,21].

The intestinal microbiota and host ensures symbiotic relationship which when disturbed can disrupt gut barrier, induce metabolic endotoxemia and low-grade chronic inflammation due to the influx of inflammatory bacterial fragments into circulation. In addition, certain bacterial species interact with host metabolism through metabolite-mediated stimulation of enteric hormones. This causes considerable knock-on effects for host adiposity and insulin resistance [22].

The incidence and onset of T1D through innate immune mechanism in an animal model has been suggested to link with alteration in the gut microbiota due to mode of birth, diet, infections, and medication including antibiotics [23].

REASON II - DIETS MODIFIES GUT MICROBIAL POPULATIONS

Imbalance diet and lifestyle may change gut flora that possibly may link metabolic disease in future. Breastfeeding children develop *B. bacterium* in their early life which produces a high amount of acetate and lactate; these metabolic by-products have suggested to restrict the growth of pathogenic bacteria in their gut [24].

Alteration in gut microbiota was achieved in an experimental animal by giving high-fat diet. This developed diabetes in the animal and supported that diet is the main factor in the development of diabetes. In this regard, emergence of specific microbial community after feeding either lipid-rich, carbohydrates-rich, or proteins rich diet in experimental animals has not been carried out [23,24]. Further, it is also suggested to undergo experimental trial considering various experimental conditions such stress, infections, antibacterial therapy, low/moderate/high physical activity, pregnancy, variant lifestyle, and climatic conditions to identify the colonized microbial community in the gut of experiment models (Fig. 1).

APPROACH TOWARD FORMULATED DIETS IN EXPERIMENTAL STUDIES

- The gut microbiota changes have been suggested in response to various modulating factors such as SCFAs, bile acids, and antibiotics. Further to reverse the adverse changes in gut could be mediated through therapeutic approach of prebiotics, probiotics and microbial transplantation in obese and diabetic humans [25].
- In a study, it shown that Gegen Qinlian decoction lessen T2D by enriching beneficial bacteria, such as *F. bacterium* spp. in gut [26].
- Similarly, transglucosidase therapy has suggested reduction in *Clostridium* and elevation in *Lactobacillus* and *B. bacterium* in T2D which further controlled blood sugar and body weight [27].

REASON III: DIABETES SPECIFIC GUT MICROBIOTA

Gut microbial analysis in diabetic patients with cirrhosis has shown higher *Bacteroidaceae* and lower *Ruminococcaceae*. Cirrhosis patients usually have shown lower in both *Bacteroidaceae* and *Ruminococcaceae* [28]. Streptozotocin-induced T1D in rats exposed noticeable shift in *Proteobacteria* especially in the ileum region and suggested that samples from these regions in gut could have more diagnostic value and therapeutic targets. In this approach, *Klebsiella* identified as markers of diagnosing T1D [29].

16s rRNA gene analysis in the stool sample of physically matched T1D and normal group explored identical *F. bacterium* sp., *Roseburia* sp., and *Bacteroides* sp. community and no significant difference [30]. Fecal sample analysis in T1D and healthy control of similar age shown a lower level of *B. bacterium* and elevated in *Enterobacteriaceae* other than *E. coli* and *C. albicans* in T1D compared to the control group explored that abnormal gut microbiota could be a triggering factor in T1D etiology [29-31].

Trillions of heterogenic gut microbes in each individual are considered in developing various metabolic disorders in response to the adaptation of diet rich, especially in fat. In T2D animal model, blood examination has shown increased levels of bacterial 16S rDNA whereas *Proteobacteria* as a tissue (blood) microbiota discovered both in healthy individuals and diabetic patients [32].

A metagenomics study in T2D revealed dysbiosis in gut due to a reduction in butyrate-producing bacteria and colonized with opportunistic pathogens. The identified microbial markers may necessitate in screening and monitoring T2D [33]. SCFAs produced in the human gut due to fermentation of macrofibrous material suggested to improve T2D features by controlling blood glucose, improving insulin action, reducing inflammation and promoting Glucagon-like peptide-1 secretion [34].

Transfer of gut microbiota from diabetes protected mice delayed the onset of diabetes by reducing insulitis and significantly altered the gut microbiome that increased *Lachnospiraceae* and *Clostridiaceae* whereas decreased *Lactobacillaceae*. This approach brought the concept of

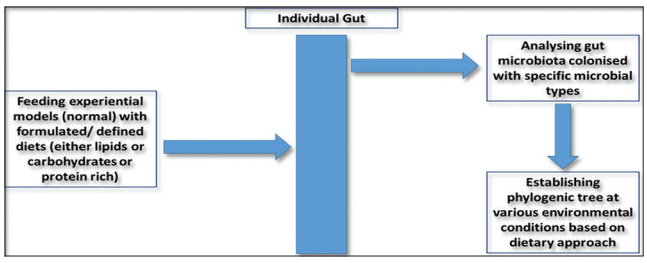

Fig. 1: Strategy to analyze gut microbiota

maintaining healthy gut and mucosal immunity which further may prevent development of autoimmune diabetes [35].

DNA study in a stool sample of T2D who separately undergone laparoscopic Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) surgery revealed more *Firmicutes* and *Actinobacteria* phyla and lesser *Bacteroidetes* phyla in RYGB group; unlikely more *Bacteroidetes* phyla found in SG group; similar *Roseburia* species was noticed in both groups [36].

Phlorizin found in fruits carries bioactive compounds that show antidiabetic activity through sodium-glucose symporters inhibition. In animal model, it had been illustrated hypoglycemic action of phlorizin along with remarkable changes in gut community with advantageous bacteria that lowered LPS and elevated SCFs [37].

A key to understand an indirect connection between dietary nutrients, host immunity, and gut microbial community that together promote systemic-metabolic inflammation provoking energy harvesting, insulin resistance, dysglycemia, T2D, and obesity have to be addressed and clarified at the earliest [38].

The recent evidence of trimethylamine (TMA) present in certain foods is metabolized to TMA N-oxide by a certain group of gut microbiota. This metabolite has been screened in animal as well as human subjects contributing the development of atherosclerosis, cardiovascular diseases, and T2D [39]. Comparative study of intestinal microbiota in normal and T2D human suggested significant differences in microbial population. Real-time quantitative PCR of V4 region of the 16S rRNA gene study in fecal sample illustrated significantly elevated *Betaproteobacteria* and reduced *Firmicutes* and *Clostridia* in diabetic group [40].

Fecal sample study using real-time quantitative polymerase chain reaction in diabetic children highlighted reduction in *Lactobacillus, B. bacterium, Blautia coccoides/Eubacterium rectale* group, *Prevotella*, *Actinobacteria,* and *Firmicutes*; elevation in *Clostridium*, *Bacteroides*, *Veillonella,* and *Bacteroidetes*. This study had given clue to the development of T1D in children [41,42]. In this regard, an approach to find the category of microbes in diabetic gut that are common in all cases are required to target for its treatment (Fig. 2).

DISCUSSION

DM has become a major public health concern. Changes in the gut microbiome composition have suggested to produce predominant metabolic diseases such as T2D and obesity due to overgrowth of microorganisms that efficiently obtain enormous energy from eaten diet. Diet probably triggers at some point to develop DM in a person's life, but it's not the sole cause. Toxins produced by bacteria may trigger the symptoms of T2D. The mechanisms of relating altered microbiota in producing insulin resistance, gut permeability, endotoxemia and

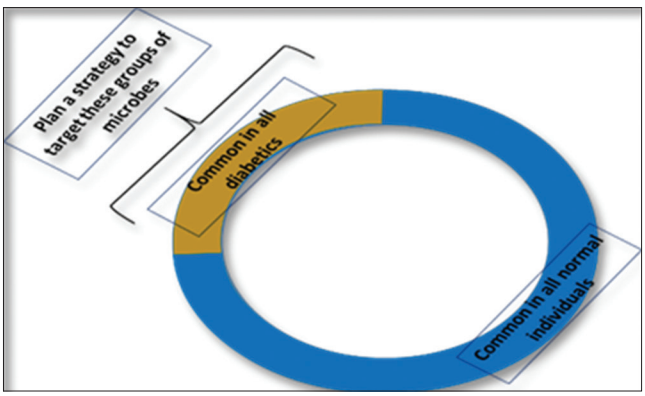

Fig. 2: Microbial phylogenetic tree

effect on bile acids action, and brown adipose tissue proportion has been remarked. New approach to minimize the consequence the harmful effect by an attempt that reverses the mechanism of insulin resistance, T2D and obesity have been appreciated through the use of pro and prebiotics, transplant of appropriate gut microbiota and intake of suitable antibiotic therapy [42]. Obesity-associated disorders are the most common health concern which develops due to misbalance in food intake and energy expenditure. Here also, it is suggested that altered composition of gut microbiota in an individual expected to be the major factor which develops obesity and associated disorders like T2D. To understand the pathogenesis, gut microbial profiling has become the biggest approach in clinical medicine to develop suitable therapies. The microbiota that impairs energy homeostasis, insulin resistance, incretins secretion and butyrate production, provoke metabolic endotoxemia and develops particular diseases are required to be identified to decrease mortality rate [43]. An approach of gut microbiota modulation as a therapeutic strategy has been suggested as a newest discoveries to prevent metabolic disorders, atherosclerosis, cardiac diseases, T2D, and Obesity [44]. The pathogenic association of gut microbiota in the development of obesity-related diseases have suggested so that possible action to prevent and treat the consequences can be undertaken. Treatment of T1D has been suggested through probiotics based new therapeutics to resolve the changes in gut microbiota due to multiple factors [45,46].

CONCLUSION

The interaction and association between gut microbiota and homeostasis as well as in the inflammation have been established. There are a number of factors which plays an important role in the establishment and maintenance of gut microbiota. This review highlighted that a special type of gut microbiota plays crucial role in diabetes development. The diabetogenic microbes in gut are required to be characterized and further targeted therapy may be introduced to prevent complications. A lot more research to be done to unzip the hormonal, immunomodulatory, and metabolic mechanisms associated with intermicrobial and host-microbes and the specific genes which are deciphers the health benefit derived from gut microbes and probiotics.

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