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Original Article

The Gut Microbiome and Diabetes Mellitus Associated Obesity: Insights into Metabolic Dysfunction and Therapeutic Targets

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ABSTRACT

Diabetes mellitus, especially T2DM, is common and depends on eating habits, lack of physical activity and obesity. DM has numerous antecedents, the most notable of which is obesity, which causes metabolic syndrome that reduces insulin sensitivity and leads to deterioration of beta cell functions. New studies on metabolic diseases emphasize that the gut microbiome is of great importance in obesity and DM development. It is estimated that the human gastrointestinal tract contains up to 100 trillion microorganisms, collectively referred to as the gut microbiota. The gut microbiota plays an important role in the development of DM and associated metabolic disorders such as obesity and insulin resistance; If there is a dysregulation, it is called dysbiosis. The aim of this review is to examine the relationship between gut microbiota and DM, with particular emphasis on the relationship between gut microbiota dysbiosis and metabolic disorders. In addition, the prospects for using microbiome-specific therapy as additional approaches to the treatment of DM and obesity comorbidities are evaluated. Understanding the impact of the gut microbiome on metabolic health is an essential step toward developing new strategies to reduce the burden of DM and obesity worldwide.

Keywords: Diabetes mellitus, Obesity, Microorganisms, Microbiome, Dysbiosis, Diseases

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INTRODUCTION

Diabetes mellitus (DM) is a long-term condition, where blood sugar levels are elevated because the body does not use insulin properly (Non-insulin dependent diabetes or Type 2, T2DM) or does not produce insulin in response to sugar (Insulin dependent diabetes or Type 1, T1DM). Global incidence of DM has remained high and T2DM accounts for over 90% of cases (IDF, 2017). This increase is absolutely linked to such factors as unhealthful diet, physical inactivity and being overweight. The human gastrointestinal tract is home to trillions of microorganisms among them bacterium, viruses, and fungi, from where they contribute to host metabolism, immune function, and overall health (Tilg & Moschen, 2014). The microbiome has recently been found to be involved in metabolic diseases, including obesity and diabetes, though such as inflammation and glucose metabolism (Knip & Siljander, 2016).

Obesity is a global problem that causes the development of DM among people, including children (Hotamisligil, 2006). It causes both macrovascular and microvascular complications hence can be described as an exhaustive burden to

healthcare systems. We know for sure that individuals categorized as having obesity have a significantly higher risk of developing metabolic syndrome according to Eckel et al., (2005), this is a state of having increased waist circumference, hypertension, dyslipidemia, and insulin resistance. The obesity that exists in adipose tissue, the liver as well as skeletal muscle impairs the action of insulin and also has an adverse effect on the beta-cells. Eight pathophysiological disturbances that contribute to T2DM are discussed and this once again proved that T2DM is a multifactorial condition, and the recognition of these disturbances should be personalised. Current data show the presence of a causal role of excess central adiposity in the pathogenesis of the metabolic syndrome although it remains to be elucidated Further (Klein et al., 2004; Fabbrini et al., 2010). Interest has now turned to the gut microbiota and its systemic attributes, and current studies revealing that obesity has affected the gut microbiota and that the latter is an environmental factor linked to adiposity and insulin resistance (Sender et al., 2016; Ningthoujam et al., 2018).

Microbiota is the microbial community in gut while microbiome is known as the total of genes of the microbiota in the gut. The human gastrointestinal tract likewise contains millions of microorganisms of different types of bacteria, viruses, fungi, phages, protozoa and others such as the archaea. The use of molecular techniques especially the 16S rRNA gene sequencing has given phylogenetic information of microbial taxa, but the advanced studies such as the shotgun metagenomic sequencing are essential (Dethlefsen et al., 2006). New calculations indicate that the number of microbes we host is as numerous as the somatic and germ cells we possess. A proposed view of our microbiota as a microbial organ living symbiotically inside the gut has provided for interlocking symbiosis with competence in the diverse activities including degradation of components of diet not utilizable by the host for energy and nutrient absorption; modulation of host immunity; integrity of the gut mucosal barrier; and xenobiotic metabolism (Bäckhed et al., 2005).

There is a synergy of several thousands of species possessing nearly 5 x 10^6 genes among them. It is dependent on a strong co-evolution and host selection; and microRNA is one of the most frequently reported compounds in mouse and human feces (Bäckhed et al., 2005). These concentrations imply that the microRNA binds to microbes and alters bacterial genes; it is understood that the amount of microRNA is inversely proportional to microbial density (Liu et al., 2016). The advancement of high-throughput sequencing methods has also led to attempts at the assessment of the intestinal metagenome according to the obtained genetic material from fecal samples, thus invoking interest in the pathogenesis of diseases (Ahmed et al., 2009).

The gut microbiota maintains a stable comparative copiousness at operative taxonomic unit levels, with five phyla dominating the microbial community: These common phyla are Actinobacteria, Firmicutes, Bacteroidetes, Proteobacteria, Verrucomicrobia (Mandal et al., 2005). High luminal turnover rate, low pH and action of secreted bile acids set up variations in microbial population at different regions of the GIT. Duodenum and Jejunum contain higher densities of Lactobacillaceae of Firmicutes and proteobacteria of Enterobacteriaceae, while distal portion contains higher densities of Firmicutes and anaerobic bacteria of Bacteroidetes (Eckburg et al., 2005).

Previous research based on metagenomic-wide association studies has revealed associations of different metagenomic data depending on whether the examined subjects are metabolically healthy or metabolically unhealthy. Among the large cohorts Human Microbiome Project (HMP), LIFELINES and the Flemish Gut flora cohorts are the highest cohorts that

contain high throughput metagenomic data that is the record of human microbiota (Rothschild et al., 2018). In normal individuals and small sets of control data, there is a boundary value, scientifically proven correlation between human metabolism and the basic composition of the intestinal microbiota.

Components of the gut microbiota and the host immune system have been interacting reciprocally in a highly dramatic way with regards to immunology. This dynamic development of the host immune system and gut microbiome defines the host–microbe relation and moderates the predisposition to infection, inflammation and autoimmunity (Lee & Mazmanian, 2010). Some of the forces that determine the formation of the microbiome include mode of delivery, breastfeeding or use of formula milk and the time of introducing solid foods (Ulfath et al., 2016). In adulthood, a person's microbiome is changed due to the alterations in the diet and the medications used. However, only 18.7% out of all interpersonal variation relates to the host characteristics, previous diseases and medications, smoking and diet (Zhernakova et al., 2016). This review seeks to establish an interpretation of the role of gut microbiome in DM, the function of dysbiosis in metabolic disorder and whether treatment involving the gut microbiome has possibilities.

The Gut Microbiome in Health

Composition of the Gut Microbiome: The human gut microbiome primarily consists of two bacterial phyla: Firmicutes and Bacteroidetes (Qin et al., 2010). Other phyla include Actinobacteria and Proteobacteria are found in smaller proportions. It has a role in opportunistic fermentation of dietary fibre, the generation of SCFAs, and biosynthesis of critical vitamins (Table 1).

Table 1: Fundamental microbial changes seen in DM and their possible roles in contributing to metabolic dysfunction.

Microbiome Component	Observed Changes in Diabetes Mellitus	Role in Metabolism and Diabetes
Firmicutes	Increased Firmicutes/Bacteroidetes ratio in T2DM	Tend to enhance the production of energy from the diet, may lead to obesity and insulin resistance (Larsen et al., 2010).
Bacteroidetes	Lowered levels in individuals with T2DM	Lower enterotypes may decrease the generation of SCFAs with glucose metabolic role (Qin et al., 2012).
Akkermansia muciniphila	Lowered abundance in diabetic patients	Is involved in the maintenance of the intestinal barrier and the reduction of inflammation; its down regulation is associated with metabolic disorders (Dao et al., 2016).
Lactobacillus species	Lowered abundance in T2DM	Lactose fermenting probiotic species that have the potential to positively impact positively IBD, inflammation and insulin resistance (Zhao et al., 2018).
Ruminococcus species	Raised abundance in individuals with T2DM	Certain organisms have been associated with impaired barrier function of the gut liner and induction of low-grade inflammation leading to

		metabolical derailment (Vrieze et al., 2012).
Faecalibacterium prausnitzii	Reduced abundance in T2DM	The anti-inflammatory capability, and synthesis of butyrate which is usually a SCFA relevant in retaining intestinal and insulin homeostasis (Tilg & Moschen, 2014).
Bifidobacterium species	Lowered abundance in T2DM	Involved in carbohydrate and SCFM synthesis and their level is inversely associated with glucose homeostasis (Cani et al., 2008).
Prevotella species	Reduced abundance in diabetes	It is known for the conversion of complex carbohydrates into SCFAs, support healthy gut (Larsen et al., 2010).
Proteobacteria	Increased abundance in people with T2DM	Markedly related to inflammation and disorder of the gut barrier; elevated levels may predispose to systemic inflammation and insulin resistance (Larsen et al., 2010).
Roseburia species	Decreased levels in T2DM	Butyrate producing bacteria involve in mucosal barrier and moderation of inflammation in the gut (Canfora et al., 2015).

Microbiome Functions: Ingested food are another source of substrates of the gut microbiota, producing small molecules that may be directly utilised by hepatocytes through uptake and transport in the portal bloodstream. These small molecules thus move around the whole body of the host and elicit a variety of host physiological changes (Roy et al., 2006). An example includes that gut microbes can produce individual metabolites for instance short-chain fatty acids (SCFA) that was discovered to provide at least 5-10% energy intake (Tilg & Moschen, 2014). The microbiome controls general metabolic activity in the gut, for instance, carbohydrate fermentation, SCFAs synthesis, and the immune response (Rooks & Garrett, 2016). Some SCFAs, butyrate, acetate, and propionate keep the insulin sensitivity and the integrity of the gut barrier (Canfora, et al. 2015). Iron is a crucial substrate; the SCFA concentration falls when the cecal SCFA concentration decreases, including propionate and butyrate. But, when iron replacement is done, then it raises the cecal butyrate concentration sharply (Dostal et al., 2012).

Dysbiosis and Diabetes Mellitus

Gut dysbiosis refers to a state in which the structure and function of the microbiota is skewed into a pathophysiological state (Le Chatelier et al., 2013). Perturbation in the microbiome known as dysbiosis has been associated with increased inflammation and impaired glycemic control in the instance of diabetes. The individuals with T2DM have distinct gut microbiota composition, increased Firmicutes-to-Bacteroidetes ratio, lowered microbial diversity, and the presence of opportunistic pathogenic strains (Larsen et al., 2010). Some of the alterations might be linked with insulin resistance and glucose intolerance mechanisms.

Mechanisms Linking Dysbiosis to Metabolic Dysfunction in Obesity:

Increased Intestinal Permeability: The intestinal microbiota is a huge metacommunity whereby species of microbes migrate from one gut space to another. Lowered gut microbial diversity is correlated with obesity and impaired insulin signaling, NAFLD and mild inflammation. The presented research outcomes indicate that glucose is indispensable for preserving the integrity of the intestinal barrier (Fig 1). Hyperglycemia results in the change of homeostatic epithelial barrier which in turn facilitates enhancement of immune-stimulatory microbial products as well as grounding for the distribution of enteric pathogens (Thaiss et al., 2018). High glucose concentration in clientele results to retrograde glucose uptake through GLUT 2 in intestinal epithelial cells hence changing the glucose metabolism within the cells and altering their genetic expression. Among the most affected pathways, there is a protein N-glycosylation in the endoplasmic reticulum and Golgi apparatus. A high-glucose diet might have an impact on the Intestinal epithelial cells which can result in changes in barrier properties (Thaiss et al., 2018). More studies are required to more fully elucidate these physiological effects.

Inflammation: The relationship between dysbiosis and pathogenesis of T2DM is mediated through chronic low-grade inflammation. Low bacterial diversity entails production of pro-inflammatory such as reduced butyrate producing bacteria and high mucin degrading bacteria which can compromise intestinal barrier function and cause low grade endotoxin mediated inflammation (Tilg & Moschen, 2014). Intestinal permeability caused by low-grade inflammation allows for the permeability of the tight junctions of the intestinal mucosa, thus the translocation of bacterial endotoxins such as LPS. This can result in systemic inflammation which can be the cause of insulin resistance (Cani et al., 2008). A relationship between low-grade inflammation often linked with elevated numbers of Gram-negative bacteria and patients suffering from T2D has also been established (Cani et al., 2008). The plasma LPS from the Gram-negative bacteria's membrane is elevated in T2DM patients. This condition is known as metabolic endotoxemia, and it is caused by bacteria translocating across the intestinal wall or, in some cases, by bacteria capsule fragments entering the bloodstream (Creely et al. 2007). Other mechanisms through which inflammation evoked by LPS activates toll like receptor 4 (TLR4) signaling pathways leads to insulin resistance (Velloso et al., 2015).

SCFAs: Gut bacteria generated SCFAs by the fermentation of dietary fibre are the playing profound roles in safeguarding glucose homoeostasis and improvement of insulin sensitivity. Imbalance typically leads to low SCFA levels also affecting diabetic control (Canfora et al., 2015). Obesity is linked to the ‘signature’ of gut microbiota, and obese animals contain larger amounts of propionate than lean counterparts. SCFAs also act as ‘ligands’, by interacting with two G-protein-coupled receptors, Gpr41 and Gpr43, modulating metabolism and inhibiting insulin signaling in adipose tissue (Samuel et al., 2008). Therefore, the SCFA of intestinal origin have been identified as a crucial source of energy and, at the same time, SCFA can act as signaling molecules in adipose tissue that regulate energy balance.

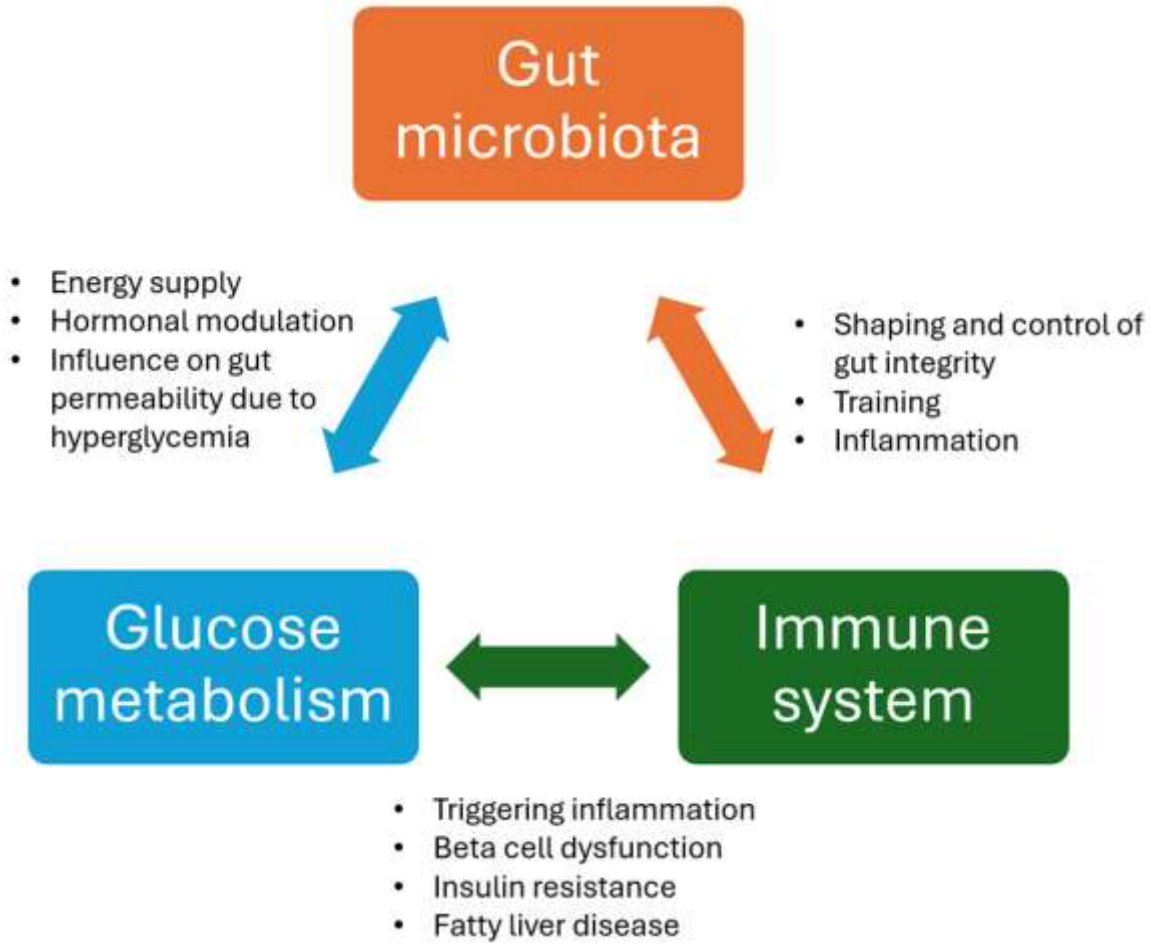

Figure 1: The role of gut microbiota in triggering inflammation

Gut Microbiome as a Therapeutic Target

Probiotics: Probiotics are live microorganisms that intend to restore the balance of the gut microbiota. Randomised controlled trials reveal that probiotics enhance insulin level, decrease inflammation, and alter glycaemic control in DM (Vrieze et al., 2012). Supplementation with probiotics in T2DM patients is found to be beneficial in ameliorating the cardiovascular risk factors through glycemic and inflammation profile (Kasińska & Drzewoski, 2015). The mechanism of action may include rising fasting insulin concentration to lower fasting plasma glucose, raising HDL and lowering TC, TG, LDL to resolve lipid feature and lowering systolic and diastolic pressure to normal. Most of the research has reported positive effects of the probiotic formulations but on some occasions. The issues which are normally founded in clinical studies comprise sample size, preparation, monitoring, sampling, inconsistency in measures, questionnaire bios and study protocol. More well-controlled studies are needed to elucidate the relationship between the functions of the microbiome, the modulation of host microbiota by probiotics and glycaemic management (Nikbakht et al., 2018). However, it has the problem of strain dependency and inter-individual variability with respect to the efficacy of the consumed probiotics.

Prebiotics: Prebiotics like inulin, fructooligosaccharides that encourage the growth of the commensal gut bacteria. It has been well documented that prebiotic increases SCFA levels and has a positive effect on glycemic regulation and reduces inflammation in T2DM (Slavin, 2013). Through the energy yield hypothesis, it is

understood that pathogenic microbiomes strip energy out of food, resulting in obesity over time. SCFAs act via the G-protein coupled receptors (GPR) that relate with degradation of lipids and glucose. SCFAs modulates the proteins such as GPR41 and GPR43 which are present on adipocytes and enter the endocrine L cells. Activation of GPR41 in the intestine promotes the time the food takes to spend in the intestine and reduce hunger. It also suppresses inflammation by stimulating intestinal GPR43 and synopsising glucagon-like peptide (GLP), a hormone of efficient insulin secretion. Enteroendocrine L cells secrete GLP-1 and the gut-trophic hormone GLP-2 which plays influential role in regulation of the gut fence system and reduces LPS translocation. However, more studies are required in order establish the implications on long-term metabolic health.

Fecal Microbiota Transplantation (FMT): FMT is a process by which fecal material from screened donor is transplanted into the patient for the purpose of reinventing the healthy flora of the gut. Several pilot observations indicate that FMT enhances insulin sensitivity and glucose tolerance in patient with metabolic syndrome, however, these results should be replicated (Vrieze et al., 2012). Lack of Bacteroidetes and Firmicutes were observed in patient colonic microbiota before FMT, However, the recipient microbiota was near to donor at two weeks following FMT and it was dominated by Bacteroides spp. Such changes were associated with the resolution of symptoms and were of a lasting nature (Borgia et al., 2015).

Dietary Interventions: The gut microbiome's composition can actually improve glucose metabolism through dietary approaches. Diets high in prebiotic fiber increase the production of short-chain fatty acids (SCFAs) and insulin sensitivity. Keto diets, on the other hand, change the composition of gut microbiota to improve metabolic health. (Deehan et al., 2018).

Future Directions and Challenges

The obesity-associated gut microbiota dysbiosis leads to the distinct gut 'fingerprint' that can change with the status of metabolic regulation, offering more opportunities for study and intervention. Though, they have been performed mostly in animals and those are significantly different in metabolism, gut microbiota, and immunity. Ethnic differences in study populations, sequencing and analytical techniques and diet variability are some of the issues that abound in research analysis (Li et al., 2017). For these problems to be studied, large prospective cohort studies should be conducted, as well as tracking of patients with pre-diabetes and diabetes, their diet, metabolic parameters, drugs, and inflammation. After discovery of some of the pathways influenced by microbiota, new therapeutic agents can be developed.

Future diabetes treatment strategies can be based on the microbiome. Since the microbial profile of the population differs, even within present-day individuals, the use of probiotics, prebiotics, and diets may be particular to every consumer (Koh & Bäckhed, 2017). Metagenomics, metabolomics, systems biology knowledge is aiding scientific investigation of the complex relations between gut microbiome – the host metabolisms. These technologies are essential for seeking novel therapeutic signature and biomarkers for diabetes (Rooks & Garrett, 2016). However, there is still some difficulty with the application of microbiome-based therapies: there is a lack of long-term clinical trials that would show effectiveness; individual differences in the microbiota; and a lack of understanding of the connection between changes in the microbiota and a person's metabolism (Marchesi et al., 2016).

CONCLUSION

There is evidence that microbiome dysbiosis affects metabolic function and systemic inflammation in diabetes mellitus. Intestinal permeability, including dysbiosis, relates to chronic inflammation and impaired glucose metabolism, so the use of the gut microbiome as a therapeutic target is apparent. The interventions, changing the gut microbiome through microbiota-directed therapies such as probiotics, prebiotics, FMT, and dietary changes, could work toward enhancing glycemic control and developing less diabetes. Prebiotics or introduction of useful bacterial strains is one of the treatments that was used, and its effectiveness measured. Supplementation with SCFAs particularly butyrate will be made in interventional studies to assess their impact on food intake, energy expenditure as well as enhanced metabolic profile in man. Fresh bacterial strains that may be suitable for administration as probiotics has been identified by FMT and these improves the rate of insulin resistance amongst metabolically syndromal males. Nevertheless, FMT procedures should follow highly standardized formats to allow for the attainment of safety and quality on multisite procedures. Therefore, the ability of human gut microbiota to change metabolic syndrome makes the modulation of this process very attractive. Microbial profiling on a metagenomic base and enumeration of singular alterations and defects represent a deterministic approach to targets of therapeutic elimination and to successful individualized strategies. More studies have to be conducted to ascertain the detailed mechanism through which the gut microbiome influences diabetes and the best ways to make the microbiome-based interventions efficient in organizing diabetes for patients.

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