Review Article

Role of Gut Microbiota on Diabetes Mellitus

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Abstract: Gut microbiota (GMB) occupy the body at birth with the newborn swallowing microbacteria from the birth canal, and evolve with aging. Bacteria make up most of the gut microorganisms and up to 60% of the dry fecal mass. The GMB is consist of of ~100 trillion bacteria, 10-fold the number of cells in the human body. The collective genome of these bacteria (microbiome) is 150-fold larger than the human genome. Whereas, the preservation of normal microbiota is encouraged by lower modulatory levels of controlling T cells secreting IL-10 and transforming growth factor beta (TGFβ), which decrease inflammation [22]. In addition, the mutualistic reaction to be related to a variability of regulatory T-cells subsets in a real-life gut flora, inclusive of symbiotic, commensal with the probable to become pathogenic, and pathogenic microorganisms. In that complicated situation, Bacteroidetes species reduce intestinal inflammation and promote regulatory T cells induction. However, these replies support the preservation of self-tolerance, and suggest a key role of probiotics in preserving a healthier intestinal microbiota.

Keywords: Gut microbiota, Bacteroidetes, Type I Diabetes Mellitus, Type II Diabetes Mellitus.

GUT MICROBIOTA

Gut microbiota (GMB) occupy the body at birth with the newborn swallowing microbacteria from the birth canal, and evolve with aging [1]. Bacteria make up most of the gut microorganisms and up to 60% of the dry fecal mass [2]. The GMB is consist of of ~100 trillion bacteria, 10-fold the number of cells in the human body. The collective genome of these bacteria (microbiome) is 150-fold larger than the human genome. These bacteria are from ~500 species with 99% belonging to 30 - 40 species from the four main families (phyla), i.e. *Firmicutes* (64%), *Bacteroidetes* (23%), *Proteobacteria* (8%), and *Actinobacteria* (3%) [3].

The human body offers favorable environment and diet to microbacteria in the lumen and bowel mucosal area. The human host affects GMB survival by dietary contents and the use of prebiotics, probiotics, and antibiotics [4]. Mutually, GMB abundance, composition, and function allow nutrient absorption, processing of vitamins, hormones, drugs, and, removal of carcinogens and probably influences longevity [5]. Disturbance of healthy symbiotic relationship results in gut *dysbiosis* that is suggested as a contributing factor to obesity and its consequences like Type 2 Diabetes Miletus (Type 2 DM), Cardiovascular Disease (CVD) and cancer [6]. Dysbiotic bacteria preserve a vicious cycle by increasing efficiency of energy harvesting from the diet. GMB dysbiosis augment shedding of lipopolysaccharide endotoxin (LPS), a molecule from the outer surface membrane of Gram (-) bacteria. It is suggested that LPS destruct gut mucosal immunity and the mucosal barrier, creating a "leaky-gut" and activates inflammatory pathways [7]. Subclinical inflammation from "dys-nutrition" and dysbiosis could continue the vicious cycle with the double-hit of steatosis (ectopic fat accumulation) with inflammation (i.e. "-itis") resulting in steato-pancreatitis (e.g, Type 2 DM), steato-arteritis (e.g. CVD), steato-hepatitis, and among other conditions [8].

The co-risks of Type 2 DM and obesity are genetics and lifestyle modifications. While genetic tendency is typically reflected "non-modifiable," the microbiome (microbiota genes) could probably be altered by lifestyle and nutrition including pre- and probiotics, and GMB thus offering a novel approach to the management of metabolic disorders [9].

Gut microbiota and Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus

Type 1 diabetes mellitus (Type 1 DM) consequences from autoimmune destruction of pancreatic β cells in genetically predisposed individuals [10]. β cell destruction involves innate and adaptive immune responses, and when approximate 80% of the pancreatic β cells are affected, the first signs of diabetes become established [11]. At this point insulin therapy is required.

The intestinal mucosa is a main site for microorganism attack: when not damaged, it protects the first line of defense against foreign substance. The intestinal wall is made up of a mucus layer, antimicrobial protecting peptides, IgA-secreting cells, and a complex system of epithelial barrier molded by adhesion and tight junctions [12]. The intestinal microbiota is ability to modulating the immune system and subsequently autoimmunity; the influence of intestinal bacteria in the pathogenesis of Type 1 DM has been established [13].

Augmented intestinal permeability may facilitate the absorption of antigens which can damage pancreatic β cells [14]. Individuals susceptible to Type 1 DM and other autoimmune diseases present defectively functioning intestinal barrier, allowing greater exposure of antigens to the immune system. Type 1 DM patients show perturbations in the structure of tight junctions as result of decreased zonulin expression, a protein associated to the regulation of intestinal permeability, and increased paracellular space between intestinal epithelial cells [15].

Pathogenic organism or, Antigens facilitated by increased intestinal penetrability, activate inflammation and immune responses, which may lead to destruction of pancreatic β cells [16]. Moreover, changes in intestinal microbiota may leads to altered inflammatory responses, a significant occurrence in the pathogenesis of autoimmune diseases such as Type 1 DM [17].

Recent studies in humans have shown that destruction of the immune system in the pancreatic β cells. Interferons produced in infectious responses and inflammatory accelerate the destruction of pancreatic β cells by inducing the expression of Major Histocompatibility Class I (MHC class I) [18]. Higher expression of CD8+ T cells and MHC class I epitopes have been observed in the pancreas of Type 1 DM persons. CD4 and CD8+ T cells are related to the pathogenesis of T1D, once CD4+ may attack pancreatic islets, and CD8+ may initiate destruction of β cell [19].

Furthermore, studies concentrating on specific bacterial lineages have exposed that Bacteroides fragilis, a member of the Bacteroidetes phyla, has ability to decrease intestinal inflammation, whilst segmented filamentous bacteria are able to activate interleukin-17 (IL-17)-producing CD4+ T helper cells (TH17), which stimulate autoimmune responses and the synthesis of inflammatory cytokines [20]. Interestingly, TH17 synthesis is dependent upon the person's genetic background [21].

Whereas, the preservation of normal microbiota is encouraged by lower modulatory levels of controlling T cells secreting IL-10 and transforming growth factor beta (TGFβ), which decrease inflammation [22]. In addition, the mutualistic reaction to be related to a variability of regulatory T-cells subsets in a real-life gut flora, inclusive of symbiotic, commensal with the probable to become pathogenic, and pathogenic microorganisms. In that complicated situation, Bacteroidetes species reduce intestinal inflammation and promote regulatory T cells induction. However, these replies support the preservation of self-tolerance, and suggest a key role of probiotics in preserving a healthier intestinal microbiota [23].

Gut microbiota and Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus (Type 2 DM) is characterized by insulin resistance in peripheral tissue and defect of insulin secretory by beta cells. Insulin receptor, glucose transporter and post-receptor perturbations are observed in Type 2 DM. Ultimately, peripheral tissues exposed to prolonged compensatory hyperinsulinemia become resistant to insulin [24]. Recently, the gut microbiota is related with the development of metabolic diseases, as diabetic and obese persons' present perturbations in the proportions of Firmicutes, Bacteroidetes and Proteobacterias [25].

Human present sterile gastrointestinal tract at birth and their microbiota is progressively added up after birth through the physical contact with the mother's breast and the surroundings [26]. Newborns' gut microbiota is mostly consisting of Bifidobacteria and Enterobacteria, and it changes progressively into a more complex arrangement, observed in adults [27]. These microorganisms and their metabolites act together with the intestinal epithelial cells in the large intestine and small intestine. Such microbiological and biochemical variations are contributed to the separate anatomical features of these two organs, and also to the mucus synthesis by goblet cells. Mucus acts as bacterial insulator at intestinal barrier level, but do not inhibit bacterial fragments to cross over the intestinal barrier. Such phenomenon contributes the maintenance of the intestinal barrier through innate and adaptive immune responses [28].

Nutrition is essential for maintenance of the intestinal microbiota, additional of nutrients like saturated and polyunsaturated fatty acids or shortage of oligosaccharides and phytochemicals can alter the bacterial metabolic activity [29]. High fat diets alter the intestinal microbiota, results in increased intestinal penetrability and susceptibility to microbial antigens, which finally associates with the incidence of metabolic endotoxemia and insulin resistance [30]. Whereas, typical diet enhances fatty acid oxidation in the liver and adipose tissue, the reactive oxygen species (ROS) generated reduces mucus synthesis in the intestinal epithelium. Thus, the damage intestinal barrier integrity allows the translocation of intestinal bacteria [31]. Furthermore, production of malondialdehyde as result of polyunsaturated fatty acid oxidation stimulate damage to the epithelial cell membranes, increasing intestinal tight junction penetrability [32].

On the other hand, Diabetic persons have lower counts of Bifidobacterium and Faecalibacterium prausnitzii, both of them Gram + with anti-inflammatory properties [33]. Recently, one study revealed that acute inflammation induced by intravenous administration of LPS stimulates metabolic endotoxemia and systemic insulin resistance, following variation of specific adipose inflammatory and insulin signaling pathways [34]. Concomitant with metabolic endotoxemia, translocation of bacteria from the intestinal barrier into the blood appears to development of Type 2 DM [35].

One of the common features to metabolic diseases such as Type 2 DM and obesity is a chronic inflammatory condition results in Toll-like receptors (TLR) activation by LPS, present in the cell wall of Gram– bacteria [36]. The TLRs consist of a large family of cell membrane proteins present in various types of cells, identifying microbe-associated molecular patterns (MAMPs) at the time of inflammatory response. TLRs play a significant role in the innate immune system due to their capability to identify the presence and nature of pathogens, providing the first line of host defense. Moreover, TLRs also stimulate adaptive immunity, once they induce the secretion of inflammatory cytokines [37]. These receptors feature leucine-rich repeat (LRR) extracellular domains, and Toll/interleukin-1 receptor (TIR) intracellular domains [38].

Toll-like receptors 4 (TLR4) are existent in tissues targeted for insulin actions. Such actions may become consists upon TLR4 stimulation, through activation of cytokine signaling cascades together with increased concentration of reactive oxygen species (ROS) [39]. Reduced Bifidobacterium due to high-fat diet ingestion has been related with higher concentrations of LPS, one of the features of metabolic endotoxemia [40]. A high-fat diet ingestion stimulates the death of Gram– bacteria, contributing to LPS synthesis in the gut and its translocation into intestinal barriers and then general circulation. Such outcome results in higher concentrations of pro-inflammatory cytokines in different tissues via TLR4 activation [41].

In addition, Inflammation levels are essential for intestinal microbiota regulation and for the progress of insulin resistance. Initiation of inflammatory pathways induced by LPS-TLR4 increases the expression of inducible nitric oxide synthase, stimulating the S-nitrosation/ Snitrosylation occurrence [42]. The generated nitric oxide reacts with cysteine remains to form adducts of Snitrosothiols, inhibiting the insulin transduction signal via phosphorylation of insulin receptor 1 substrate (IRS-1) in serine, which results in insulin resistance in muscle, hepatic, and adipose tissue [43]. Others studies have shown that pro-inflammatory cytokines induce phosphorylation of IRS-1 in serine, whose initiation may cause inhibition of insulin receptor tyrosine kinase and protein kinase B (AKT) signaling, also increasing the degradation of IRS-1 [44].

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