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Enteric microbiome and Diabetes mellitus

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The complex relationship between diabetes, obesity and gut microbiota is being released with emerging evidence. Investigation of human microbiome is the most rapidly expanding field in biomedicine. Enteric microbes are key players in the management of glucose homeostasis in humans. There is unmet need to clear all related mechanisms so as to develop new therapeutic approaches for people with diabetes mellitus.

The term "microbiome" refers to the totality of microbes colonizing humans and their genes[1]. The gastrointestinal tract harbors about 100 trillion microbes including archaea, bacteria protozoans, viruses and fungi. *Formicates* such as Lactobacillus, Ruminococcus and Clostridium species, as well as *Bacteroidetes* and *Actinobacteria* account for the largest proportion of microbiota.

The enteric microbiome achieves very important physiological functions: protection against pathogens, synthesis of vitamins, immune system development, promotion of intestinal angiogenesis and fat storage, digestion of complex carbohydrates and SCFA production[2]. The gut-hypothalamus axis is influenced by microbes through hormones and neurotransmitter release in order to regulate food intake and energy balance[3].

Carbohydrates are the primary sources of energy for both the human host and their microbes. Humans lack enzymes for digestion of complex carbs including cellulose, xylans, resistant starch and inulin. Microbiome encode enzymes required for indigested carbohydrates fermentation. The latter harvests energy for microbial growth and produces monosaccharides and short-chain fatty acids (SCFAs), which act as ligands for G protein-coupled receptors GP41 and GP43 which are abundant in adipose tissue, intestinal epithelial and immune cells. SCFAs have significant effects on the gut wall health as a source of energy, anti-inflammation agents, vasodilators, promotility agents and wound healing components. Butyrate is principally used as an energy source for enterocytes, whereas acetate and propionate are used by the liver for lipogenesis and glyconeogenesis.

The gastrointestinal tract microbiome is affected by host nutrition, environment and host genetics and thus it develops obesity related metabolic disorders such as diabetes mellitus. The term "dysbiosis" refers to pathological alterations in the gut microbiota and is

generally induced by high fat diet[4]. Dysbiosis enhances energy harvest through a change in the Bacteroidetes/Firmicutes ratio. Altered microbial composition –characterized by poor species richness and diversity– provokes distorted SCFAs profile and consequently less expression of G-protein receptors leading to poor energy homeostasis, obesity, insulin resistance and type 2 diabetes mellitus (T2DM).

Microbiome-triggered chronic low-grade inflammation is another important causal factor for T2DM. Symbiosis impairs intestinal wall integrity and high mucosal permeability causes translocation of endotoxins (lipopolysaccharides – LPS) from the lumen to the systemic circulation. End toxemia leads to low-grade inflammation, autoimmunity and oxidative stress that probably induce beta cell destruction and insulin resistance. In terms of autoimmunity, LPS stimulates innate immune responses by activating CD14, nucleotide oligomerization domain (NOD) and toll-like receptor 4 (TLR4) at the surface of dendritic cells and macrophages[5].

Type 1 diabetes mellitus (T1DM) is probably caused by a chronic inflammatory disease of the gastrointestinal tract in hereditary prone individuals, leading to autoimmune destruction of β-islet cells[6]. The disease is associated with microbiome symbiosis. A higher proportion of *Actinobacteria, Bacteroidetes* and *Proteobacteria* is distinctive of T1DM[7]. A second possible mechanism for the enteric microbiota to induce T1DM is that gut leakiness, endotoxemia and low-grade inflammation initiates immune deregulation[8]. Oxidative stress might be a third pathogenic factor caused by microbial dysbiosis[9]. It is still uncertain if these microbiome-related metabolic oxidative stress, autoimmunity and low-grade inflammation act independently or together.

Several studies concerning the role of bile acids, GABA and endocannabinoid system in the pathogenesis of T2DM have been so far published. Sex hormones observed to affect autoimmunity in early life and subsequently cause T1DM. But these studies were conducted with mice and not with humans, so as much work has to be done furthermore.

Microbial dysbiosis is associated with gestational diabetes mellitus due to impaired intestinal barrier and thus endotoxemia.

Metformin is one of the most prescribed oral antidiabetics. Although this regimen does not administer to modify gut microbiota, there is a growing evidence that some effects are attributed to changes in microbiome composition. Metformin induces a higher abundance of the mucin degrading bacterium *Akkermansia muciniphilla* leading to gut barrier be more resilient. In humans, metformin seems to reduce intestinal lipid absorption and LPS-triggered local inflammation as an effect of modified enteric microbiome[10].

Metabolic surgery, specifically RYGB markedly altered the composition of the distal gut microbiota in mice, 1 week after surgery. A decrease in body weight, improved insulin sensitivity and reduced fasting triglyceride levels were documented. RYGB leads to a specific spectrum of microbiota per se[11]. These findings need to be corroborated in humans.

Administration of probiotics has a beneficial role in the management of T2DM, since they significantly decreased FPG and HbA1c in diabetic patients[12]. Probiotics also showed anti-inflammatory and anti-oxidative effects in diabetic patients. Findings still imply a need for well-designed clinical trials. Probiotic approaches in T1DM aim more on the modulation of the diabetes risk in stages with HLA−susceptibility or antibody formation than in manifest disease. Lactobacillus species negatively correlated with T1DM development. Diabetes-rone rats administered L. johnsonii developed T1DM at a protracted rate[13]. Further proposed targets for a probiotic therapy in T2DM include the endocannabinoid system and GABA.

Many animal experiments where gut microbiome was transferred between individuals have already been published. In humans with metabolic syndrome, only one study –designed to treat– has been so far reported[14]. Improvement of peripheral insulin sensitivity and increase of the levels of butyrate-producing microbiota, such as *Roseburia intestinalis*, were noted.

For a medical doctor, the rapidly evolving field of metagenomics, is impossible to be overlooked. Although a different microbe composition in diabetic patients prevails, the patient numbers are often low, results are contradictory and methodology is different. We still lack knowledge of a normal gut microbiota. This may vary in different geographical regions, depend on different nutritional habits, gender, age, etc.

Scientific approaches focus on bacteria, while other microbes are still neglected. In T1DM, viruses

particularly coxsackie viruses infect human pancreatic β-cells. Other viruses such as rotavirus or rubella virus have been discussed in the pathogenesis of T1DM. So far, it is unknown whether fecal microbiota transplantation from a donor with a desired phenotype may not put the recipient at risk for other diseases.

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