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THE INFLUENCE OF HUMAN GASTROINTESTINAL MICROFLORA IN DEVELOPMENT OF DIABETES TYPE II

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ABSTRACT
Recent studies show that human gastrointestinal microflora has a great influence over development of diabetes type II. The current review summarizes some latest data concerning the effects of the variations in gastrointestinal microbiota, which have both positive and negative sites in development and protection of type 2 diabetes. Recent studies have shown a relationship between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes. There is an increasing body of literature that directs the attention to a possible third culprit for development of these metabolic diseases: the gut microbiota. These microorganisms and thus their bacterial genome are increasingly considered important pathogenic factors in various diseases such as inflammatory bowel disease, obesity, diabetes etc. Three bacterial divisions, the *Firmicutes* (gram positive), *Bacteroidetes* (gram-negative) and *Actinobacteria* (gram positive) dominate the adult human gut microbiota. Overweight and diabetes are associated with different groups of the intestinal microflora.

Key words: intestinal microflora, type 2 diabetes, obesity, microbiota

INTRODUCTION

The human intestinal tract contains a large variety of microorganisms, of which bacteria are the most dominant and diverse. As a whole, the gut microbiome (the genome of gut microorganisms) is more than 100-fold larger than the human genome [1]. Thus, intestinal microbiota can be viewed as an 'exteriorised organ' that contributes to overall metabolism and plays a role in converting food into nutrients and energy. The community of at least 1014 bacteria is dominated by anaerobic bacteria and composed of 500 to 1000 different species [2].

Recent studies based on large-scale 16S rRNA gene sequencing and more limited techniques, based on quantitative real time PCR (qPCR) and fluorescent in situ hybridization (FISH), have shown a relationship between the composition of the intestinal microbiota and metabolic diseases like obesity and diabetes. Type 2 diabetes is a metabolic disease which primary cause is obesity-linked insulin resistance [3]. More than several hundreds of millions of people will be diabetic and obese over the next decades. Metabolic diseases such as diabetes and obesity are becoming a social problem of utmost importance for all countries [4]. However, some other factors like mental stress, infection and genetic predisposition might lead to diabetes as well [5, 6]. Both obesity and diabetes are characterized by a state of chronic low-grade inflammation with abnormal expression and production of multiple inflammatory mediators such as tumor necrosis factor (TNFs) and interleukins (ILs) [7].

Over the last decade, diabetes has been the cause of lethal cardiovascular events. Cardiovascular diseases with lethal outcome have progressed the most, since 62% increase has been quantified in Western countries where diabetes and obesity have strongly emerged.

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Preventive strategies, most likely based on a change in dietary habits or the use of food complements prebiotic and probiotic, could be massively launched [8].

Recent studies have characterized the gut microbiota in type 2 diabetic patients. The authors described that the proportions of phylum *Firmicutes* and class *Clostridia* were significantly reduced in the diabetic group compared to the control group [3]. Furthermore, the ratios of *Bacteroidetes* to *Firmicutes* as well as the ratios of *Bacteroides-Prevotella* group to *C. coccoides-E. rectale* group correlated positively and significantly with plasma glucose concentration. Therefore, bacterial sequences, specific for type 2 diabetes rather than obesity can be considered as signatures of hyperglycemic syndrome [4].

Many of the mechanistic studies have mainly focused on the biology of relationships between various human organs and cell systems. In contrast, geneticists have mainly focused on the human genome and they attempt to unravel the risk factors for type II diabetes mellitus.

Nevertheless, there is an increasing body of literature that directs the attention to a possible third culprit: the gut microbiota. These microorganisms and thus their bacterial genome are increasingly considered important pathogenic factors in various diseases such as inflammatory bowel disease to obesity.

MOST COMMON BACTERIA OF MICROBIOTA

Three bacterial divisions, the *Firmicutes* (gram positive), *Bacteroidetes* (gram-negative) and *Actinobacteria* (gram positive) dominate the adult human gut microbiota.

The *Firmicutes* are the largest phylum include: *Lactobacillus*, *Mycoplasma*, *Bacillus* and *Clostridium*

Fetuses are sterile in uteri, but in the first year of life the infant intestinal tract progresses from sterility to extremely dense colonisation with a mixture of microbes broadly similar to that found in the adult intestine. At the age of 4 years, the gut microbiota in host individuals has fully matured [9, Burcelin, 2011 #1].

GENETIC CONNECTION

The microbiota of monozygotic twins living separately is notably more similar than the microbiota of unrelated individuals. In contrast, the environment seems to be less important, since marital partners did not have a significantly greater similarity of bacterial communities than unrelated individuals, despite the fact that these partners lived in the same environment and had similar dietary habits. The gut microbiota of an adult could be constant until 7th decade, fluctuates because of use of antibiotics [4].

MECHANISMS OF INCREASED FAT UPTAKE

Studies of germ free and control mice have also revealed that microbiota direct the host to increase hepatic triacylglycerol and glucose production. In fact, microbial colonisation of the gut might suppress expression of the fasting-induced-adipose-factor (FIAF), leading to decrease activity of lipoprotein lipase (LPL) inhibitor and hence to increased activity of LPL. Increased LPL activity promotes increased uptake of fatty acids and triacylglycerol accumulation in adipocytes [4, 9].

INFLAMATORY ORIGIN OF DIABETES AND OBESITY

Obesity and diabetes are both characterised by chronic low-grade inflammation of unclear origin. In vitro and in animal models an increase in proinflammatory cytokines, such as TNF-α, has led to tissue insulin resistance. It is demonstrated that bacterial lipopolysaccaride (LPS) is a gut microbiota-related factor that triggers secretion of proinflammatory cytokines. LPS is continuously produced in the gut through lysis of gram-negative bacteria. Authors showed that continuous subcutaneous low-rate infusion of LPS led to excessive weight gain and insulin resistance in mice. Moreover, mice carrying a tall-like receptor 4 mutation (TLR4, a LPS receptor) tended to be protected against the development of insulin resistance in adipose tissue in response to a high-fat diet [10]. It has been showed that high-fat diet decreases the number of bifidobacteria and increases plasma LPS [3]. Also it has been demonstrated that modulation of gut microbiota, e.g. by antibiotic treatment or dietary intervention with oligofructoses, reduced glucose intolerance, decreased body weight gain and inhibited inflammation in mice [3, Cani, 2011 #5].

These findings suggest that changes in the gut microbiota could be responsible for increased endotoxaemia in response to a high-fat diet, which in turn would trigger the development of obesity and diabetes mellitus.

The early intestinal microbial colonization at birth may impact the occurrence of metabolic diseases. Recent data suggested that the Bifidobacterial count in fecal samples during infancy, was higher in children remaining normal weight over a 7-year follow-up study [11]. Conversely, the microbiota aberrancy during infancy in children becoming overweight was associated with a greater number of *Staphylococcus aureus* [4].

A research conducted by Larsen et al shows that intestinal microbiota in humans with type 2 diabetes is different from non-diabetic persons [3]. It is demonstrated that type 2 diabetes is associated with compositional changes in the intestinal microbiota mostly apparent at phylum and class levels. The relative abundance of *Firmicutes* was significantly lower, while the proportion of *Bacteroidetes* and *Proteobacteria* was somewhat higher in diabetic persons compared to their non-diabetic counterparts. Accordingly, the ratios of *Bacteroidetes* to *Firmicutes* significantly and positively correlated with reduced glucose tolerance. Overweight and diabetes are associated with different groups of the intestinal microbiota. Bacterial groups that distinguished the diabetic from the non-diabetic microbiome included *Bacteroides-Prevotella* group versus class *Clostridia* and *C. coccoides-E.rectale* group, which ratios were significantly higher in diabetic persons [3]. The significantly higher levels of *Bacilli* and the *Lactobacillus* group in diabetic subjects compared to controls in the present study, have recently been reported in relation to type 2 diabetes in mice models and to obesity in human adults [12, 13].

Cani and coworkers [14], using mice models, proposed a hypothesis connecting metabolic diseases with the presence of Gram-negative bacteria in the gut, also offering a likely explanation of the differences between the diabetic and non-diabetic microbiomes in this study.

CONCLUSION

Obesity and its associated diseases such as type 2 diabetes are increasing at an alarming rate. During the past years, the discovery of the roles of the gut microbiota in energy homeostasis raised the question of whether commensal gastrointestinal bacteria have their positive or negative side in development and protection of type 2 diabetes. Hopefully, in the near future it will be possible to identify whether certain profiles of gut microbiota or particular microbiota functionalities are a friend or foe of metabolic health. This would allow the design of proper diagnostic tools and therapeutic strategies to treat the consequences caused by dysbiosis between the gut microbiota and its host.

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