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Metagenomics Health Claim: Are you Rich Enough in your Gut Micro biota?

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Abstract

Distinct alterations in the composition of the gut microbiota have been observed in obese individuals, patients with type 2 diabetes and other disease-states associated with obesity. Microbial 'gene richness' revealed by metagenomics studies appears to be a robust indicator of health status. These studies are summarized in this commentary with a prospect on 'clinical metagenomics'.

Keywords: Metagenomics; Microbial gene richness; Obesity; Type 2 diabetes; Lifestyle modification

Introduction

Experimental data in animals, but also observational studies in humans, suggest that the composition of the gut microbiota differs in obese versus lean individuals. Distinct alterations in the composition of the gut microbiota have also been observed in patients with type 2 diabetes compared to normal glucose tolerant individuals. Accumulating evidence suggests that this is also true in patients presenting other diseases associated with obesity or nutritional imbalance, such as non-alcoholic fatty liver disease (NAFLD), liver cirrhosis or cardiovascular diseases. Paradoxically, some individuals seem to be more susceptible to develop obesity or are more resistant to weight loss during dietary restriction or lifestyle modification measures. How do you explain all of these? Let's see what microbes (metagenomics) tell us.

Microbial 'Gene Richness' Revealed By Metagenomics

Over the last few years, new molecular techniques (metagenomics) have accumulated a wealth of data about the commensal microbes in the gut. Studies by the MetaHIT [1] and MicroObes consortium [2] published in Nature at the end of the year 2013, are two important contributions in the field of metagenomics and its translational applications. Using different sequencing technology, these studies detected a bimodal distribution of microbial genes. Researchers stratified the studied population based on 'gene richness' as "low gene count" (LGC) and "high gene count" (HGC) categories according to the number of genes harbored in their gut microbiota and thereby different microbial communities. MetaHIT consortium focused on a cohort of 292 Danish adults, comprising 123 non-obese and 169 obese subjects. Through quantitative metagenomics, it was found that two groups of people can be distinguished by the richness of bacteria they carry and the abundance of certain bacterial species. A quarter of the cohort is "poor" in bacteria, whereas the rest is "rich". In this study, individuals with a LGC (23% of the population) were characterized by more marked weight-gain over time, adiposity, insulin resistance and inflammation when compared with HGC individuals. More interestingly, the abundance of specific taxa were significantly associated with bacterial richness and thereby the phenotype. For instance, 36 genera were significantly associated with HGC, and among these genera at least 4 of them (Faecalibacterium prausnitzii, Akkermansia muciniphila, Bifidobacterium spp., and Lactobacillus spp.) have been previously shown in the literature [3-5] to be associated with an improved gut barrier function, reduced body weight or improved glucose and lipid metabolism. Conversely, Le Chatelier et al. [1] have also noted that specific genera known to be associated with inflammatory phenotype or altered gut barrier function were associated with LGC. The authors also demonstrate that analysis of just a few bacterial marker species was sufficient to distinguish between high and low bacterial richness. The French consortium Microbes study [2] comprised of a cohort of 49 French obese or overweight persons, also confirms the results of the MetaHIT study. The low or high bacterial communities are similar in both French and Danes. Moreover, it is possible to differentiate the "rich" communities from the "poor" ones with only six typical bacterial species, with an accuracy of 95%. Individuals with reduced microbial gene richness (40%) were present with more pronounced dys-metabolism and low-grade inflammation. Interestingly, based on the abundance of certain cluster of bacterial species and gene richness, it has been shown possible to characterize and distinguish patients with type 2 diabetes [6] and liver cirrhosis [7]. Cotillard et al. [2] monitored gut microbe profiles during diet-induced weight loss and weight stabilization interventions in obese or overweight individuals. In this study, the impact of a diet (high in protein and fiber, and low in calories) was on the richness of the gut microbiota. This diet, after 6 weeks, led to not only an expected improvement of the clinical characteristics of the individuals under study, but also to an increase of the richness within the poor group. Dietary intervention seems to be less efficient for inflammation variables in individuals with lower gene richness. This study also reported that increased consumption of high-fibre foods, such as fruit and vegetables, leads to an increase in bacterial richness and improves some clinical symptoms associated with obesity. Very recently [8], a healthier dietary pattern (lower consumption of confectionary and sugary drinks, and highest consumption of fruits but also yogurts and soups) was also shown associated with lower inflammatory markers as well as greater gut microbiota richness in overweight and obese subjects.

Taxa-Based Microbial Associations with Disease States

The bacterial composition in the gut mainly belongs to the phyla Firmicutes and Bacteroides [9]. The gut microbiota is also dominated by less abundant phyla such as Proteobacteria, Actinobacteria, and Euryarchaeota [10]. Analysis of the microbiota in humans and in animal disease models has permitted the identification of specific taxa-based microbial associations with disease states. A significant increase in the number of Clostridium, Bacteroides and Veillonella and a significant decrease in the number of Lactobacillus, Bifidobacterium, Blautia coccoides/Eubacterium rectale group and Prevotella has been observed in the children with type 1 diabetes [11]. Earlier, proportions of phylum Firmicutes and class Clostridia were shown significantly reduced in patients with type 2 diabetes compared to the control group [12]. The diversity of the microbiota as well as the abundance of Faecalibacterium prausnitzii (a prototype anti-inflammatory microbiota) has been shown significantly lower in obese patients and patients with type 2 diabetes compared with lean individuals [13]. In the study by Qin et al. [6], type 2 diabetes is characterized by a selective increase in several opportunistic pathogens and a reduction in bacteria producing beneficial metabolites, such as butyrate. Indeed, it's well known that butyrate may exert a protective role, enhancing the expression of tight junctions genes, promoting gut barrier function and reducing bacterial traslocation [14]. Studies have also demonstrated an inverse correlation between the presence of the closely adherent mucin-degrading bacterium Akkermansia muciniphila and obesity in humans [15] and A. muciniphila abundance has been shown reduced in obese and type 2 diabetic mice [4]. At this context, it is interesting to note that metformin treatment also increases Akkermansia concentrations accompanied by its metabolic benefits [16]. These studies raise hope for selective (both taxa and phylum based) targeting and manipulation of gut microbiota for metabolic benefits. Short chain fatty acids (SCFAs), especially butyrate and propionate have evolved as attractive pathways to how the microbiota might shape immunological and metabolic functions and these should be beneficially exploited for newer therapeutic measures.

Microbial Promo (!) For Bariatric Surgery

Roux-en-Y gastric bypass (RYGB) surgery is one of the most efficient procedures for treating morbid obesity and results in weight-loss and improvements in metabolism and inflammation. Differential adaption of gut microbiota to bariatric surgery-induced weight loss was demonstrated by Furet et al. [17] and certain specific bacterial groups were considered as possible factors associated with changes in nutritional status along with metabolic and inflammatory parameters. Distinct intra-individual changes in microbiome composition and gene function with an improvement in metabolic and inflammatory parameters were also demonstrated after RYGB in obese patients with type 2 diabetes [18]. Interestingly, the study by Kong et al. [19] demonstrated that the richness of gut microbiota increased after RYGB and the variations of bacterial genera were correlated with changes in both clinical phenotype and adipose tissue gene expression. Almost half of the correlations were independent of the change in calorie intake. These findings stimulate and warrant deeper explorations of the mechanisms linking gut microbiome and adipose tissue pathological alterations in human obesity and its changes after weight loss. Different bariatric surgical techniques causes weight loss and diabetes remission to varying degrees and recent studies point out a role of distinct changes in microbiota composition [20] which needs to be studied in-depth by future investigations.

Lifestyle Modifications and Metagenomics Benefits

There is growing awareness that diet and lifestyle choices have a profound impact on the gut microbiota [21]. While the composition of the gut microbiota is the determinant of the efficacy of energy harvest from food [22], the composition of the diet we consume is also known to affect the microbial community composition [23]. Korpela et al. [24] have presented evidence that it is possible to identify obese individuals who will benefit most from a simple dietary intervention based on the gut microbiota composition before the intervention. What about the impact of both exercise and dietary changes on gut microbiota? A remarkable study by Clarke et al. [25] demonstrated the impact of exercise and associated dietary changes on the gut microbiota by studying a professional Rugby team undergoing rigorous training program compared to healthy non-athletes. In this study, microbiota diversity measures positively correlated with protein intake and plasma creatine kinase levels (a marker of extreme exercise), which suggested that both diet and exercise were driving the changes in microbial diversity. Exercise has been shown to prevent weight gain and alter the gut microbiota in a mouse model of high fat diet-induced obesity [26]. Study by Petriz et al. [27] also demonstrated that obese rats harbor a different gut microbiota compared to non-obese rats and that exercise training alters gut microbiota from an obese genotype background. As exercise increases gut microbiota richness/ diversity, it appears as an important factor in the complex relationship among the host, host immunity and the microbiota. The 'Western microbiota' concept recently discussed by Sonnenburg and Sonnenburg [28] implies that the present day Western lifestyle with a diet low in microbiota-accessible carbohydrates (MACs), might have selected for a microbiota with altered membership and functionality in certain individuals compared to those of groups living traditional lifestyles. It is suggested that the low-MAC Western diet might result in poor production of gut microbiota-generated metabolites including short-chain fatty acids (SCFAs), alter glucose & lipid metabolism and predispose individuals to metabolic diseases.

Future Perspectives

The resilience of the mircobiota and the capability to maintain a well established equilibrium between symbionts and potential pathogens is certain to be determining factors in shaping health or disease. Disturbances in the gut microbiota (dysbiosis) could be an early warning sign for metabolic diseases including type 2 diabetes and the recent studies support this notion as specific microbial fingerprints and their metabolites are expected to reliably predict disease risk in the host. Although further studies are needed, the fact that the simplest but robust molecular index (the gut microbial genes richness), was correlated with metabolic markers [1] and was prognostic to weight loss during low caloric diet over time [2] and the demonstration that exercise and associated dietary extremes impact on gut microbial diversity [25] is a proof of evidence for future applications of clinical metagenomics. The major challenge will be to determine how specific bacterial groups or their microbial activities can be harnessed for prevention of disease(s) including type 2 diabetes with dietary/physical activity changes and also targeted for future therapeutic strategies for better health outcomes. As recently reviewed by Druart et al. [29], changes in the composition and/or activity of the gut microbiota by administration of nutrients with probiotic or prebiotic properties are

expected to modulate host gene expression and metabolism and thereby positively influence host tissue homeostasis and related metabolic disorders. However, additional studies and randomized controlled human trials using probiotics and prebiotics with adequate efficacy and safety profiles are needed to further understand their clinical impact on gut microbiota manipulation. To conclude, better health may not directly be related to how rich you are (financially)… but it's going to be related to how rich you are in your gut microbiota! Therefore the new advice for both the general public and the patients is this– 'stock up on your good gut bacteria!' The road to personalized gut microbiota management might be seen long and winding, but the destiny makes it worthwhile with a futuristic research and development investment.

Duality of Interest

The author declares that there is no duality of interest associated with this manuscript.

Contribution Statement

The author is the sole contributor to this paper.

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