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Review

The role of microbiome in determining pediatric health

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Proceedings

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The last ten years, the next ten years in Neonatology
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Abstract

The beneficial effects of food containing probiotics (or prebiotics or synbiotics) on human health – and in particular of dairy products such as yogurt and milk – are increasingly being promoted by food manufacturers, but also by health professionals. The human microbiome is composed of bacteria, viruses, fungi, archaea and protozoa. Each body site has its own distinct microbiome, with a unique microbial composition that presumably reflects the differences in tissue structure and function. Shifts in the composition of the gastrointestinal microbiome have been linked to the development and progression of several intestinal and extra-intestinal diseases, including childhood asthma development and inflammatory bowel disease. Probiotics are advertised to contribute to overall well-being and are sought to prevent and alleviate many diseases, especially digestive, immunological and respiratory disorders. Modulating microbial exposure through probiotic supplementation represents a long-held strategy towards ameliorating disease via intestinal microbial community restructuring. Several recent human trials have demonstrated the potential for live biotherapeutic products in disease management and prevention, but larger, better controlled, and universally standardized studies are needed for the rigorous scientific evaluation of probiotic therapies and the comparison of diametric outcomes.

Keywords

Microbiome, probiotics, Pediatrics, gastrointestinal tract, bacteria, dysbiosis.

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Introduction

The concept of microbial ingestion to manipulate the microbial ensemble in our intestine for the benefit of human health is not novel. Eli Metchnikoff hypothesized that consumption of lactic-acid-producing bacteria (LAB), such as lactobacilli found in yogurt, enhanced longevity [1]. The word 'probiotic' (meaning 'for life') was probably first used in 1953 by Werner Kollath to describe organic and inorganic food supplements applied to restore health to patients suffering from malnutrition and to distinguish these 'pro-biotics' from anti-biotics [2]. A formal definition of probiotics was formulated in 2001 by the advisory body of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), and this definition has been widely utilized during the past 12 years. This definition states that probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [3]. The beneficial effects of food containing probiotics on human health – and in particular of dairy products such as yogurt and milk – are increasingly being promoted by food manufacturers, but also by health professionals. Probiotics are advertised to contribute to overall well-being and are sought to prevent and alleviate many diseases, especially digestive, immunological and respiratory disorders. Nevertheless, regulatory bodies of the US and Europe have recently restricted label claims that were made without rigorous scientific support. This has prompted expanded research efforts in the field to better understand the efficacy of these food products in promoting human health. *Lactobacillus* and *Bifidobacteria* species represent the microbes most commonly researched for conferring health benefits. Other LAB (*Streptococcus* spp. and *Enterococcus* spp.) as well as a strain of *E. coli* Nissle 1917, some *Bacilli*, and even the yeast *Saccharomyces cerevisiae subsp. boulardii* (often referred to as "*Saccharomyces boulardii*") have been studied for their use as probiotics [4]. The emergence of investigations concerning the nature and mechanisms of probiosis and the rapid coalescence of the human microbiome research community globally since 2005 [5] provided the foundation for the current era in metagenomics. This field has rapidly expanded to embrace the many commensal and beneficial microbes that may contribute to human health and disease prevention. Now, with decreased costs of DNA sequencing and improved bioinformatic tools, we can compare gastrointestinal (GI) tract bacterial communities among individuals, of all ages from infancy to adulthood [6]. Some key recent findings are that the initial bacterial community, even in the GI tract, depends strongly on delivery mode; the process of early development of the microbiota is highly unstable and idiosyncratic and the microbiota differs considerably among children from different countries. Older adults significantly differ have substantially different GI tract communities than younger adults, indicating that the GI tract microbiota can change throughout life [6].

From a sterile environment to the microbiome

The healthy human fetus develops within an environment that is thought to be mostly sterile. However, although bacteria in the amniotic fluid are associated with preterm labor, babies exposed to bacteria in utero are often viable [7]. Human adults have highly differentiated bacterial communities in different body habitats [8, 9], although, interestingly, in newborn infants, these communities appear to be largely undifferentiated [10]. The human microbiota develops from an initial inoculum that is determined by mode of delivery. Through a dynamic process that is unique to every individual and unstable, the microbial community moves towards, but only approximates, its adult state during the first 1-3 years of life. Although the GI microbial communities of adults are often believed to be stable, there is evidence that it changes through life – at lower rates than in childhood, with unknown effects on health.

Antibiotics have a radical effect on the GI microbial community at all stages of life, and responses vary among individuals. Global use of antibiotics and disappearing indigenous lifestyles could eliminate a key source of information about the microbes with which we have evolved and perhaps

important insights into the normal developmental process.

Based on studies in humanized mice, diet can affect GI transit through microbiota-dependent or microbiota-independent pathways, depending on the type of dietary change.

GI transit time and gut microbiota are interrelated. Diet can independently affect both GI transit time and gut microbial composition and function (as determined by metabolite profiles). However, diet-induced changes in microbial composition may be mediated in part by changes in GI transit time, and the effect of diet on GI transit time may be a result of altered functionality of the gut microbial community caused by the dietary change. The effect of diet, transit time, and microbiota composition creates a highly interdependent and interactive environment. These results have implications for disorders that affect GI transit and gut microbial communities, including irritable bowel syndrome and inflammatory bowel disease [11].

A recent review discusses the structural composition of intestinal microbiota, the functional relationship between the latter and the host, and the role of abnormal microflora in chronic diseases.

A more complete view of the gut microbiota is being developed following the Human Microbiome Project. The microflora in children is plastic, susceptible to changes in response to diet modifications, antibiotic treatment and other events, providing the opportunity to study its functional role. Increasing evidence highlights the role of nutrition in the age-related development of microflora. Eubiosis, that is, a normal microflora structure, provides protection against infections, educates the immune system, ensures tolerance to foods, and contributes to nutrient digestion and energy harvest. Changes in microflora, consisting in the overpresence of harmful species or underpresence of commensal species, or dysbiosis produce dysfunctions, such as intestinal inflammation or dysmotility. Moreover abnormal pattern of microflora have been consistently detected in specific diseases.

Eubiosis and dysbiosis

A relationship exists between eubiosis and functions and conversely between dysbiosis and dysfunctions or even diseases. Abnormalities in microflora composition may trigger or contribute to specific diseases. This raises the hypothesis to target microflora in order to restore eubiosis through the use of antibiotics, probiotics or nutrients [12].

A better understanding of how the gut microbiota are assembled and maintained is increasingly relevant to the treatment of complex chronic diseases. A growing number of studies highlight the fact that certain microbiota can be harmful to host health. Alterations in microbial composition associated with human diseases have been described as examples of dysbiosis. Dysbiosis refers to differences in microbial populations that may reflect an abnormal ecological state contributing to pathology or the excess of pathogenic mechanisms within the human microbiome. Dysbioses of the microbiome are associated with an expanding list of chronic diseases that includes obesity [13], inflammatory bowel disease (IBD) [14, 15] and diabetes [16]. Studies have shown that patients with IBD harbour fewer bacteria from the phylum *Bacteroidetes*, fewer from the phylum *Firmicutes* and more from the phyla *Actinobacteria* and *Proteobacteria* than healthy subjects [17]. People with type 2 diabetes have reduced numbers of bacteria from the *Firmicutes* and instead harbour a greater proportion of bacteria belonging to the *Bacteroidetes* [16]. The microbiota of infants with necrotizing enterocolitis is composed of members of the *Proteobacteria* and *Firmicutes* only, whereas healthy infants also harbour species from the *Bacteroidetes* and *Fusobacteria* [18]. These types of correlative observations raise the question of whether the microbiota has a causative role in disease, or whether dysbiosis is a by-product of the disease. For several diseases, recent work shows the answer to be that the microbiota does contribute to disease. Transplantation experiments in which the microbiota of a diseased animal is grafted into a germ-free healthy recipient have demonstrated that several disease phenotypes could be transferred by the microbiota. These include excess adiposity [19], metabolic syndrome [20] and colitis [21], all of which are traits of complex diseases that are also affected by host genetic and environmental factors. Several studies have shown the potential efficacy of probiotics for the treatment of different pediatric diseases. Numerous probiotics have yielded success in the prevention of severe NEC and all-cause mortality in premature infants, including very-low-birth-weight infants [22, 23]. Many studies in children have demonstrated that probiotics may be effective at suppressing antibiotic-associated diarrhea [24, 25]. The American Academy of Pediatrics (AAP) endorsed the application of probiotics for the prevention of antibiotic-associated diarrhea in healthy children [26]. Contraddictory

results have been obtained in pediatric IBD trials. There are insufficient data to recommend probiotics in ulcerative colitis or Crohn's disease, while good evidence supports the use of specific probiotics for maintenance of remission in pouchitis [27]. The demonstration of differences in the fecal microbiome such as relative deficiencies of the genera *Bifidobacterium* and *Verrucomicrobium* in children with Irritable Bowel Syndrome (IBS), diarrheal predominant subtype, has suggested the potential role of probiotics in the treatement of this disorder [28]. Guandalini et al. in 2010 showed the relative success of a *Bifidobacterium-Lactobacillus* combination strategy [29].

Conclusions and future directions

The consumption of probiotics, for both health maintenance and disease alleviation is gaining popularity with consumers and is increasing advocated by health care professionals. Although our knowledge about human microbial composition is rapidly developing, many gaps exist about the functional capacity and metabolic machinery of the human microbiome. Although more studies are needed, probiotics appear capable of affecting the composition and function of the microbiome. Several recent human trials have demonstrated the potential for live biotherapeutic products in disease management and prevention.

An enhanced understanding of the effects of probiotics on the microbiome should facilitate selection of optimal probiotic strains for specific diseases. Larger, better controlled, and universally standardized studies are needed for the rigorous scientific evaluation of probiotic therapies. Future studies should focus on the effects of specific probiotic strains on the human microbiome. By understanding how probiotic strains alter specific functions of the human microbiome at different body sites, probiotic strain selection may be optimized for specific disease states.

Declaration of interest

Prof. Annamaria Staiano is consultant for DMG Italy and speaker for Valeas.

References

1. Metchnikoff E. In The Prolongation of Life: Optimistic Studies. Edited by Mitchell PC. New York & London: G.P. Putnam's Sons, 1908.
2. Hamilton-Miller JM, Gibson GR, Bruck W. Some insights into the derivation and early uses of the word 'probiotic'. Br J Nutr. 2003;90:845.
3. United Nations, Guidelines for the Evaluation of Probiotics in Food. Edited by UNFAO/WHO. London, Ontario, Canada, 2002
4. Sanders ME, Gibson GR, Gill H, Guarner F. Probiotics in food: their potential to impact human health.Council for Agricultural Science and Technology (CAST). 2007.
5. NIH HMP Working Group; Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, Bonazzi V, McEwen JE, Wetterstrand KA, Deal C, Baker CC, Di Francesco V, Howcroft TK, Karp RW, Lunsford RD, Wellington CR, Belachew T, Wright M, Giblin C, David H, Mills M, Salomon R, Mullins C, Akolkar B, Begg L, Davis C, Grandison L, Humble M, Khalsa J, Little AR, Peavy H, Pontzer C, Portnoy M, Sayre MH, Starke-Reed P, Zakhari S, Read J, Watson B, Guyer M. The NIH human microbiome project. Genome Res. 2009;19(1):2317-23.
6. Dominguez-Bello MG, Blaser MJ, Ley RE, Knight R. Development of the human gastrointestinal microbiota and insights from high-throughput sequencing. Gastroenterology. 2011;140:1713-9.
7. Di Giulio DB, Romero R, Amogan HP, Kusanovic JP, Bik EM, Gotsch F, Kim CJ, Erez O, Edwin S, Relman DA. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS One. 2008;3(8):e3056.
8. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nat Rev Microbiol. 2008;6(10):776-88.
9. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science. 2009;326(5960):1694-7.
10. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA. 2010;107(26):11971-5.
11. Kashyap PC, Marcobal A, Ursell LK Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, Tache Y, Pasricha PJ, Knight R, Farrugia G, Sonnenburg JL. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. Gastroenterology. 2013;144(5): 967-77.
12. Buccigrossi V, Nicastro E, Guarino A. Functions of intestinal microflora in children. Curr Opin Gastroenterol. 2013;29(1):31-8.
13. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480-4.
14. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA. 2007;104(34):13780-5.
15. Sartor RB. Microbial influences in inflammatory bowel diseases. Gastroenterology. 2008;134:577-94.

16. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;5(2):e9085.
17. Peterson DA, Frank DN, Pace NR, Gordon JI. Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. Cell Host Microbe. 2008;3(6):417-27
18. Wang Y, Hoenig JD, Malin KJ, Qamar S, Petrof EO, Sun J, Antonopoulos DA, Chang EB, Claud EC. 16S rRNA gene-based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. ISME J. 2009;3(8):944-54.
19. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008;3(4):213-23.
20. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010:328(5975):228-31.
21. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, Glickman JN, Glimcher LH. Communicable ulcerative colitis induced by T bet deficiency in the innate immune system. Cell. 2007;131(1):33-45.
22. Mihatsch WA, Braegger CP, Decsi T, Kolacek S, Lanzinger H, Mayer B, Moreno LA, Pohlandt F, Puntis J, Shamir R, Stadtmüller U, Szajewska H, Turck D, van Goudoever JB. Critical systematic review of the level of evidence for routine use of probiotics for reduction of mortality and prevention of necrotizing enterocolitis and sepsis in preterm infants. Clin Nutr. 2012;31(1):6-15.
23. Downard CD, Renaud E, St Peter SD, Abdullah F, Islam S, Saito JM, Blakely ML, Huang EY, Arca MJ, Cassidy L, Aspelund G; 2012 American Pediatric Surgical Association Outcomes Clinical Trials Committee. Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2012;47(11):2111-22.
24. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. Gastroenterology. 2009;136:2015-31.
25. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2013;5:CD006095.
26. Thomas DW, Greer FR. Probiotics and prebiotics in pediatrics. Pediatrics. 2010;126:1217-31.
27. Guandalini S. Update on the role of probiotics in the therapy of pediatric inflammatory bowel disease. Expert Rev Clin Immunol. 2010;6:47-54.
28. Rigsbee L, Agans R, Shankar V, Kenche H, Khamis HJ, Michail S, Paliy O. Quantitative profiling of gut microbiota of children with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol. 2012;107:1740-51.
29. Guandalini S, Magazzù G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, Sibal A, Romano C, Canani RB, Lionetti P, Setty M. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51(1): 24-30.