MICROBIOTA

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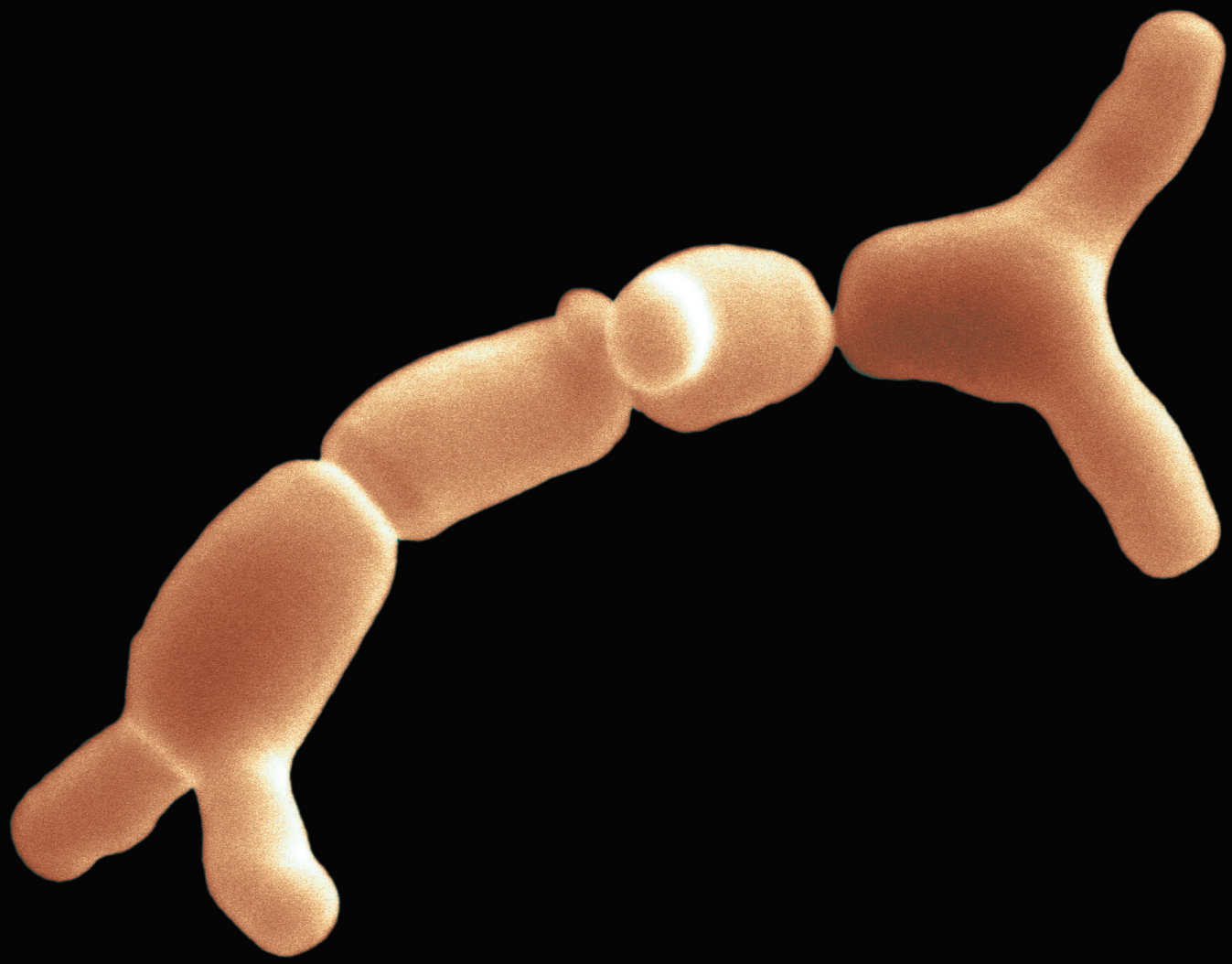

BIOCODEX Microbiota Institute

SUMMARY

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Dear readers, the World Health Organization (WHO) defines overweight and obesity as the abnormal or excessive accumulation of fat that presents a risk to health. Determined using the Body Mass Index (BMI), obesity affects indiscriminately children and adults, men and women, in both high and low-income countries. The prevalence of this condition has almost tripled between 1975 and 2016, and it has become a major public health challenge in the 21st century. For several years the WHO has been conducting campaigns and action plans to increase the awareness of populations and governments in the various countries about the condition and how to prevent it. However, up to now these have had little success and not a single country has managed to contain the phenomenon.

Obesity is caused by an imbalance between the number of calories consumed and those expended, further induced and/or reinforced by a diet composed of high-calorie, high-fat and processed foods and a sedentary lifestyle characterised by low levels of physical activity. In addition to its recognition as being a potential disability in the workplace by the European Court of Justice in 2014, obesity also has multiple health consequences.

The concept of a 'metabolic syndrome' emerged several years ago. This term groups together non-communicable conditions such as obesity, disorders of carbohydrate homoeostasis (oral glucose intolerance, insulin resistance, impaired fasting blood glucose and type 2 diabetes), disorders of lipid homoeostasis (dyslipidaemia) and other cardiovascular risk factors (hypertension). This metabolic syndrome doubles the risk of early mortality and triples the risk of developing cardiovascular disease.

In her summary, Professor Yolanda Sanz (Institute of Agrochemistry and Food Technology, Valencia, Spain) explains the link between metabolic diseases and intestinal micro-organisms, which play a key role in nutrient metabolism, the regulation of sugar and lipid absorption, intestinal hormone synthesis, intestinal barrier regulation and immune responses. Her summary highlights that any alteration and reduction of microbial diversity can promote obesity and metabolic inflammation - thus leading to severe comorbidities - and that a diet rich in fibre, as well as faecal microbiota transplantation and some probiotics, are ways of preventing metabolic diseases by modulating the intestinal microbiota.

> "ANY ALTERATION AND REDUCTION OF MICROBIAL DIVERSITY CAN TRIGGER OBESITY AND METABOLIC INFLAMMATION"

Microbiota is also implicated in Parkinson's disease. Professor Harry Sokol (Hôpital Saint-Antoine, Paris, France) presents the results of a study published in 2019 in *Science* which suggests that in some patients modulating the efficacy of levodopa by acting on the microbiota could be an option.

In addition to these promising 'pharmacomicrobiomic' prospects, Professor Emmanuel Mas (Children's Hospital, Toulouse, France) comments on recentworks published in *The Lancet* that mention the predictive role of the microbiota, which should now be taken into account in the therapeutic choices in children diagnosed with ulcerative colitis.

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MICROBIOTA AND METABOLIC DISEASES

Obesity is one of the greatest public health challenges of the 21st century because of its high prevalence and its role in the development of multiple non-communicable diseases (metabolic syndrome -MetS- and type 2 diabetes mellitus -T2DM). Evidence of the role of gut microbiota alterations, partly due to unhealthy diets, in the mechanisms linking obesity to inflammation and metabolic dysfunction opens new opportunities for a better understanding of the disease aetiology and for designing management strategies. The investigated paths for disease management include faecal microbiota transplants (FMT), dietary ingredients intended to nourish our beneficial microorganisms (like prebiotic fibres) and indigenous bacteria (known as probiotics) to replenish our gut with missing beneficial microorganisms. Evidence is promising but work is still needed to identify constellations of effector intestinal bacteria that help in reprograming and preventing obesity, and to personalize diets to optimize metabolic functions of our gut microbes.

By Prof. Yolanda Sanz
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OBESITY, METABOLIC SYNDROME AND DIABETES

We are witnesses of an obesity epidemic worldwide that no country has yet been able to reverse. The overall obesity prevalence has tripled in the US and many EU countries since the 1980s, becoming one of the greatest public health challenges of the 21st century (http://www.who.int). In fact, obesity shows high comorbidity rates, constituting a major risk factor for the development of multiple non-communicable diseases. Obesity-induced insulin resistance is considered a key causal factor of MetS, which often progress to pancreatic β cell failure that finally triggers T2DM onset [1].

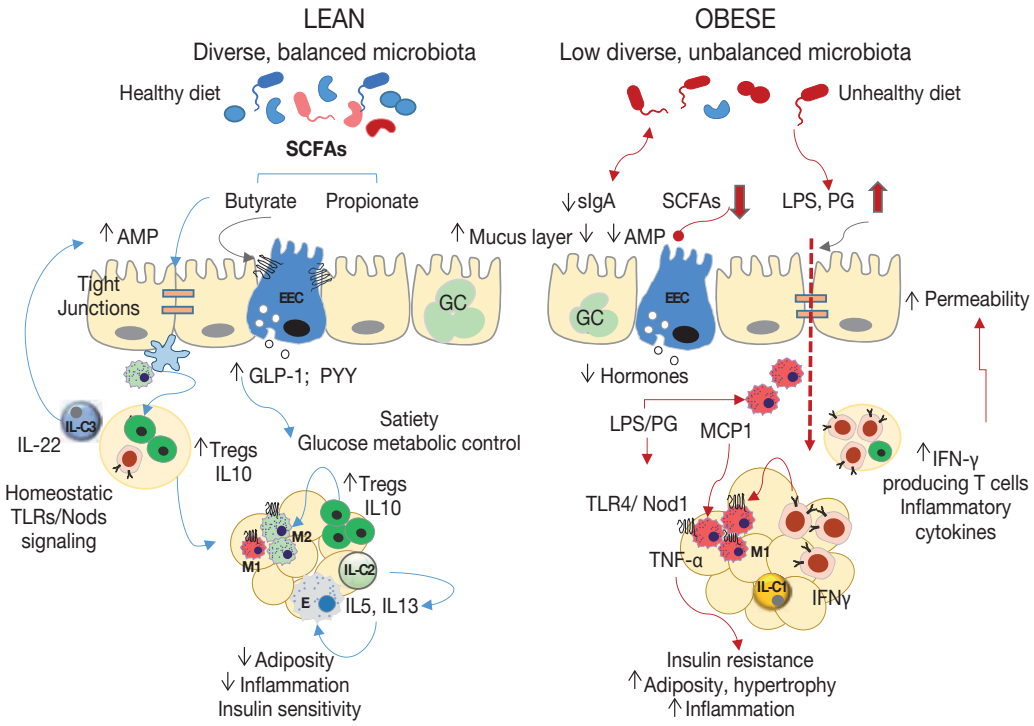
METABOLIC INFLAMMATION: THE PATH FROM OBESITY TO CHRONIC COMORBIDITIES

Currently, it is well-documented that the chronic inflammatory state associated with obesity and causally linked to metabolic complications affects the adipose tissue and other organs, including the brain, muscle, liver, pancreas and gut, which show different particularities [1, 2]. Specifically, the involvement of the intestinal immune system and the microbes that expand under the exposure to unhealthy diets have recently emerged as additional drivers of obesity-associated metabolic inflammation and could also represent therapeutic targets [2, 3].

▶ FIGURE 1

Schematic representation of the role of the gut microbiota and the diet in obesity-associated inflammation.

SCFAs: short-chain fatty acids
LPS: lipopolysaccharide
PG: peptidoglycan
sIgA: secretory immunoglobulin A
AMP: antimicrobial peptides produced by Paneth cells
ECC: enteroendocrine cells
GC: Goblet cell producers of mucus
GLP-1: Glucagon 1 peptide
PYY: peptide tyrosine tyrosine
IL: interleukin
Tregs: regulatory T cells;
M1: classically activated macrophages
M2: anti-inflammatory or alternative activated macrophages
ILC: innate lymphoid cell
TLR: Toll-like receptor
NOD: Nucleotide binding oligomerization domain protein receptor.



HOW IS THE INTESTINAL MICROBIOTA INVOLVED?

The involvement of the gut microbiota in obesity has been partly inferred from observational studies reporting dysbiosis in obese subjects compared to lean ones in cross-sectional assessments. Evidence of gut microbiota changes during dietary, medicinal or surgery interventions intended for weight loss and for improving metabolic complications allowed establishing similar relationships where obesity was associated with reductions in species diversity and increases in bacterial taxa like Proteobacteria (enterobacteria) and *Bilophila wadsworthia*.

The most consistent microbiota-based biomarker associated with obesity is a reduced diversity of bacterial species, which may also predispose to the development of obesity, chronic inflammation and metabolic complications.

By contrast, healthy metabolic phenotypes were often associated with increases in the phyla Bacteroidetes or Bacteroidetes/Firmicutes ratio or the genera *Bacteroides, Prevotella, Akkermansia, Faecalibacterium* or *Christensenella* [4, 5]. However, findings were not fully consistent across studies partly due to the heterogeneity of the studies and limitations of their designs. Further meta-analyses have indicated that the only biomarker that could be generalized for obesity was reduced bacterial species diversity [6]. It is also likely that all obese subjects cannot be categorized by the same dysbiotic pattern, particularly considering the high interindividual variability of the microbiota and complexity of the metabolic phenotypes (obesity with and without other complications). More recently, the gut microbiota alterations that precede the development of obesity have been identified as causally involved in the aetiology. Of note it is a recent longitudinal study showing that a reduced bacterial species diversity, linked to unhealthy dietary habits, provides a scenario favouring the overgrowth of Proteobacteria (enterobacteria), which precedes the development of overweight during a 4-year follow-up in children [7].

More definitive proof of a causal role of the microbiota in defining the metabolic phenotype of the subject has been achieved through FMT, where the dysbiotic microbiota from diseased subjects was transferred to new animal recipients. Most of these experiments showed that FMT was sufficient to replicate the metabolic phenotype of the donor (lean or obese) [8].

MICROBIOTA-MEDIATED MECHANISMS OF ACTION

Gut microbes influence energy metabolism through their capacity to increase the human ability to metabolize nutrients and extract calories from the diet as well as regulating the absorption of sugars and lipids and their deposition in peripheral tissues [8]. Gut microbes and their metabolic products are also involved in the regulation of the enteroendocrine system, for example, via the production of short-chain fatty acids, which induced the synthesis of intestinal hormones (*e.g.*, GLP-1, PYY) that act via endocrine and neural routes regulating appetite, food intake and glucose metabolism [9]. Moreover, the gut microbiota is a major regulator of the gut barrier and the immune system, whose alterations are implicated in obesity-associated low grade inflammation and insulin resistance as detailed below and schematized in (**Figure 1**) [2,3].

It is likely that a unique pattern of intestinal dysbiosis for obesity cannot be identified and may depend on the underlying metabolic complications and other biological and environmental features of the individual.

DEFECTIVE MUCOSAL BARRIER FUNCTION IN OBESITY

Unhealthy diets cause defects in the intestinal mucosal barrier affecting its penetrability and favouring the translocation of bacterial components, such as the bacterial lipopolysaccharide (LPS) and the peptidoglycan or even whole microorganisms, which may activate innate immunity in metabolically active organs. The defective intestinal mucosal barrier has been attributed to local inflammation caused by diets rich in saturated fat and the diet-induced dysbiosis as well as to associated disturbances in the mucus layer [10] and in antimicrobial peptides production by Paneth cells (Reg3γ, lysozyme 1) [11]. For example, increased LPS plasma levels (known as "metabolic endotoxemia") was shown to cause obesity and metabolic dysfunction in animal models and to be associated with an elevated body mass index, HF feeding, postprandial inflammation and risk of T2DM in humans. This could be favoured by the overgrowth of Gram-negative bacteria like enterobacteria, which are a source of LPS under HF feeding. LPS could activate innate immunity in the gut and beyond and induce the recruitment of inflammatory immune cells in metabolic tissues, like macrophages. Diets rich in saturated fat may also promote the growth of other Gram negative bacteria like *Bilophila wadsworthia*, which generates hydrogen sulphide, a toxic metabolite for enterocytes leading to a leaky gut, inflammation and metabolic dysfunction [12]. Finally, HF diet (HFD) may also increase circulating peptidoglycans, likely through the diet-induced changes in the expression of the antimicrobial peptide lysozyme 1 that hydrolyse components of the bacterial cell-walls. Depending on the peptidoglycan type, these could act as Nod1 ligands of pro-inflammatory macrophages of the adipose tissue or liver causing insulin resistance, while opposite effects seem to occur in pancreas beta cells, possibly as a counterbalance mechanism [13].

DYSREGULATION OF INTESTINAL IMMUNOCOMPETENT CELLS IN OBESITY

Similar to other metabolic organs, including the adipose tissue and liver, breakdown of immune homeostasis has been observed in the intestine during obesity. In diet-induced obesity diverse subsets of innate and adaptive immune cells within the gut adopt a pro-inflammatory phenotype, primarily demonstrated by increases in pro-inflammatory macrophages and cytokines (IFNγ). In parallel, there are reductions in proportions of Treg cells and type 3 ILCs producing IL-22, which help to maintain mucosal integrity and intestinal homeostasis in lean subjects [2,3]. Some of these alterations are reversed through microbiota depletion (*e.g.*, antibiotic treatment) or the administration of, for example, specific bifidobacteria that also restore diet-induced intestinal dysbiosis in obesity, supporting a causal role of the gut microbiota in metabolic inflammation [3]. Also, intestinal IgA+ immune cells act as mucosal mediators of whole-body glucose regulation in HFD-induced obesity. The HFD reduces the number of IgA+ immune cells and secretory IgA. The reduction of IgA could add another level of destabilization in the bacterial community to that caused by HFD, linked to increases in gut permeability and adipose tissue inflammation [14].

HOW MICROBIOTA MODULATION COULD IMPACT THE DISEASE EVOLUTION

FMT. A clinical trial showed that insulin sensitivity could be improved in humans with MetS 6 weeks after being transplanted with gut microbiota from a lean healthy donor [5]. An increase in microbial diversity and abundance of bacteria producing butyrate was also observed. Another trial conducted in subjects with indexes of MetS receiving the microbiota of responders to bariatric surgery reported changes in the expression of dopamine receptors, which could account for a better control of food intake, but did not confirm effects on insulin resistance. Many other trials to evaluate the effects of FMT on obesity have been registered, but the outcomes have not been published yet [5]. Therefore, scientific evidence supporting the use of this strategy to tackle obesity complications is still very limited.

Dietary fibres. Consumption of diets with fibre intake above current recommendations (25 g/day for adults) improves weight maintenance and reduces the risk of coronary heart disease and T2DM, according to a large body of evidence from humans. Some of the effects of dietary fibre are due to its physicochemical properties (*e.g.*, indigestibility, viscosity, etc.), which contribute to reducing the glycemic responses and the energy intake, and improving the blood lipid profile. Other effects could be mediated by their impact on the subject's gut microbiota, which ferments fibres generating metabolites such short chain fatty acids (SCFAs: butyrate, propionate, etc.) with an active role in the host's metabolism. SCFAs induce the production of enteroendocrine peptides (GLP-1, GLP-2, PYY) that strengthen the gut barrier, induce satiety, improve glucose metabolism and exert anti-inflammatory effects in obesity. Fibre intake also increases gut microbiota diversity which is associated with a healthy metabolic phenotype. Also, beneficial effects of fibres depend not only on the type and amount of fibre, but also on the person's microbiota structure, its diversity and the presence or absence of specific bacterial species involved in their utilization [15]. Altogether this points to the need of progressing towards more personalized dietary recommendations [15].

Beneficial bacteria. The first and second generation of probiotics: The majority of clinical efficacy trials have been conducted

Intestinal dysbiosis sustained by unhealthy diets contributes to the dysregulation of the intestinal immune system, which constitutes an additional driver of obesity-associated metabolic inflammation and also represents a therapeutic target.

▼ TABLE 1

Examples of recent clinical trials intended to prove the effects of the first generation of probiotics on metabolic health.

BACTERIAL STRAIN	STUDY GROUP/DURATION	MAIN FINDINGS	REFERENCE
Lactobacillus gasseri SBT2055	Overweigh and obese adults/12 weeks	↓ Visceral fat and body weight	[16]
Bifidobacterium animalis 420	Overweigh and obese adults/6 months	↓ Body fat in completers; no effects on per-meability or inflamma-tory makers	[17]
Bifidobacterium pseudocatenulatum CECT 7765	Obese children with insulin resistance/ 12 weeks	↑ HDL-cholesterol ↓ Inflammatory markers	[18]

▼ TABLE 2

Examples of pre-clinical and clinical trials intended to prove the effects of a second generation of probiotics on metabolic health

BACTERIAL STRAIN	TYPE OF TRIAL/STUDY GROUP	MAIN FINDINGS	REFERENCE
Bacteroides uniformis CECT 7771	Preclinical trial in mice with diet–induced obesity	↓ Body weight gain and fat mass ↑ Glucose tolerance ↓ Inflammation	[5]
Bacteroides thetaiotaomicron	Preclinical trial mice with diet–induced obesity	↓ Body weight gain and fat mass ↓ Inflammation No effects on glucose or insulin	[19]
Christensenella minuta	Germ-free mice colonized with stools of human donors plus *C. minunta*	↓ Adiposity ↑ Gut microbiota diversity	[4]
Akkermansia muciniphila	Clinical trial overweight/obese insulin-resistant volunteers/ 3 months	↑ Insulin sensitivity ↓ Plasma insulin, total cholesterol and LPS Killed bacteria (pasteurization)	[20]

with bacterial strains traditionally used as probiotics for humans, "the first generation of probiotics", which essentially include *Lactobacillus* and *Bifidobacterium*. **Table 1** summarizes some examples, although much more can be found in literature, with positive and negative outcomes.

A few attempts have also been made to isolate new bacterial species of the human indigenous microbiota, consistently associated with a healthy metabolic phenotype, with a view to create a "second generation of probiotics". These may help us to enlarge our potential to replenish the gut microbiota with missing microbes. **Table 2** summarizes some of the studies conducted in animal models (preclinical trials) and the only one conducted in humans so far.

* (www.mynewgut.eu, unpublished).

CONCLUSION

Scientific evidence confirms the role of gut microbiota alterations, partly due to unhealthy diets, in obesity and metabolic complications. Intestinal inflammation is emerging as a driver of systemic inflammation in obesity. This process is modulated by the gut microbiota and the diet, which altogether represent both a cause and a therapeutic target. Experimental trials provided proof-of-concept that a "healthy microbiota", specific intestinal bacteria or dietary fibres that potentiate their functions could play a role in obesity management. To make further progresses towards the development of tangible solutions for obesity, further efforts are still needed to identify the effector intestinal bacteria that cooperate in reprogramming obesity and to personalize diets in order to optimize gut microbiota functions in support of our metabolic health.

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COMMENTED ARTICLE
ADULTS' SECTION

By Prof. Harry Sokol
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PARKINSON'S DISEASE: DISCOVERY AND INHIBITION OF LEVODOPA METABOLISM BY GUT BACTERIA

Commentary on the original publication by Rekdal et al. (Science 2019 [1])

The human gut microbiota metabolizes the Parkinson's disease medication Levodopa (L-dopa), potentially reducing drug availability and causing side effects. However, the organisms, genes, and enzymes responsible for this activity in patients and their susceptibility to inhibition by host-targeted drugs are unknown. Here, the authors describe an interspecies pathway for gut bacterial L-dopa metabolism. Conversion of L-dopa to dopamine by a pyridoxal phosphate-dependent tyrosine decarboxylase from *Enterococcus faecalis* is followed by transformation of dopamine to m-tyramine by a molybdenum-dependent dehydroxylase from *Eggerthella lenta*. These enzymes predict drug metabolism in complex human gut microbiotas. Although a drug that targets host aromatic amino acid decarboxylase does not prevent gut microbial L-dopa decarboxylation, the authors identified a compound that inhibits this activity in Parkinson's patients microbiotas and increases L-dopa bioavailability in mice.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

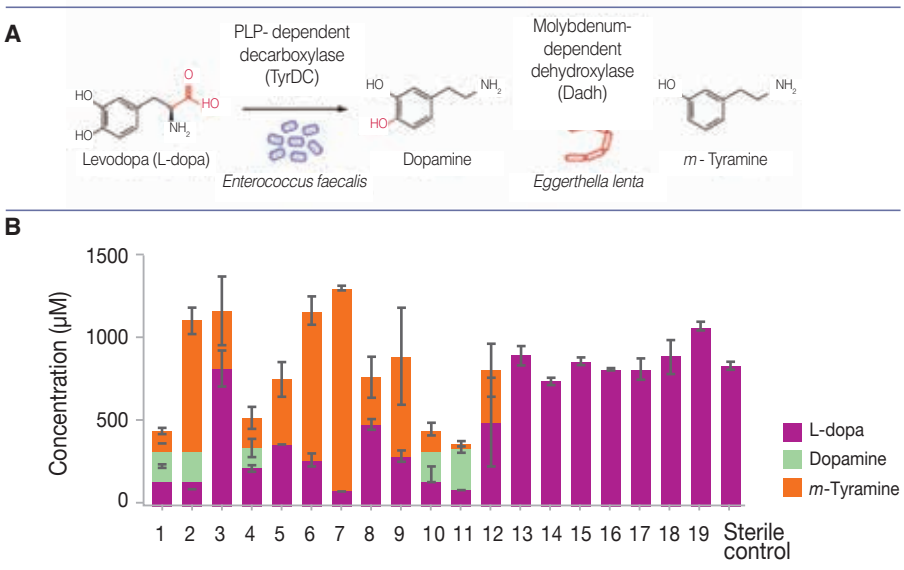
Parkinson's disease is a debilitating neurological condition affecting more than 1% of the global population aged 60 and above. The primary medication used to treat Parkinson's disease is levodopa (L-dopa) [2]. To be effective, L-dopa must enter the brain and be converted to the neurotransmitter dopamine by the human enzyme aromatic amino acid decarboxylase (AADC). However, the gastrointestinal tract is also a major site for L-dopa decarboxylation, and this metabolism is problematic because dopamine generated in the periphery cannot cross the blood-brain barrier and causes unwanted side effects. Thus, L-dopa is co-administered with drugs that block peripheral metabolism, including the AADC inhibitor carbidopa. Even with these drugs, up to 56% of L-dopa fails to reach the brain. Moreover, the efficacy and side effects of L-dopa treatment are extremely heterogeneous across Parkinson's patients, and this variability cannot be completely explained by differences in host metabolism. Previous studies in humans and animal models have demonstrated that the gut microbiota can metabolize L-dopa [3]. The major proposed pathway involves an initial decarboxylation of L-dopa to dopamine, followed by conversion of dopamine to m-tyramine by a dehydroxylation reaction. Although these metabolic activities were shown to occur in complex gut microbiota samples, the specific organisms, genes, and enzymes responsible were unknown. The effects of host-targeted inhibitors such as carbidopa on gut microbial L-dopa metabolism were also unclear. As a first step toward understanding the gut microbiota's effect on Parkinson's disease therapy, the

KEY POINTS

- Some gut bacteria can metabolize L-dopa to dopamine and then to m-tyramine, limiting its availability in the brain
- The gut microbiota plays a role in the efficacy and toxicity of L-dopa treatment for Parkinson's disease
- Use of a specific inhibitor of bacterial L-dopa metabolism can increase L-dopa bioavailability and thus enhance its efficacy

▼ FIGURE 1

Metabolism of L-dopa - A. Schematic metabolism of L-dopa by gut bacteria. **B**. Metabolism of L-dopa by 19 human fecal microbiota samples (ex vivo). Samples were cultured anaerobically with d3-phenyl-L-dopa (1 mM) for 72 hours. Mean concentration ± SEM (n=3).



authors sought to elucidate the molecular basis for gut microbial L-dopa and dopamine metabolism.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

The authors hypothesized that L-dopa decarboxylation would require a pyridoxal phosphate (PLP)-dependent enzyme. They searched gut bacterial genomes and identified a conserved tyrosine decarboxylase (TyrDC) in *Enterococcus faecalis* (**Figure 1A**). Genetic and biochemical experiments revealed that TyrDC simultaneously decarboxylates both L-dopa and its preferred substrate, tyrosine. Next, they used enrichment culturing to isolate a dopamine-dehydroxylating strain of *Eggerthella lenta* (**Figure 1A**). Transcriptomics analysis showed that the enzyme responsible for this activity is a molybdenum cofactor-dependent dopamine dehydroxylase (Dadh). Unexpectedly, the presence of this enzyme in gut bacterial genomes did not correlate with dopamine metabolism. Instead, it is a single-nucleotide polymorphism (SNP) in the *dadh* gene that predicts activity. L-dopa metabolism through this pathway was variable across subjects (**Figure 1B**). In gut microbiotas from Parkinson's patients, the abundance of *E. faecalis*, TyrDC, and the SNPs of dadh correlated with L-dopa and dopamine metabolism, confirming their relevance. The authors then showed that the human AADC inhibitor carbidopa had only a minimal effect on L-dopa decarboxylation by *E. faecalis*, and was completely ineffective in complex gut microbiotas from patients, suggesting that this drug likely does not prevent microbial L-dopa metabolism *in vivo*. Given TyrDC's preference for tyrosine, the authors examined tyrosine "mimics" and identified (S)-α-fluoromethyltyrosine (AFMT) as a selective inhibitor of gut bacterial L-dopa decarboxylation. Co-administering AFMT with L-dopa and carbidopa to mice colonized with *E. faecalis* increased the serum concentration of L-dopa.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

These findings show that the gut microbiota can metabolize L-dopa and thereby influence the effectiveness and side effects of this drug. This study paves the way towards the discovery of predictive biomarkers for L-dopa efficacy and toxicity. Furthermore, since the underlying molecular mechanisms are known, the use of specific inhibitors of gut microbial L-dopa metabolism may be possible in patients whose microbiota contains bacteria with deleterious activities.

CONCLUSION

The gut microbiota in some Parkinson's patients can metabolize L-dopa. This may underlie the heterogeneous efficacy and side effects of this treatment in Parkinson's disease. The use of inhibitors of this bacterial metabolism could offer a solution. More generally, this study provides new evidence for the role of the gut microbiota in drug pharmacokinetics and pharmacodynamics. It opens up promising prospects for a field that could be called "pharmacomicrobiomics".

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COMMENTED ARTICLE
CHILDREN'S SECTION

CLINICAL AND BIOLOGICAL PREDICTORS OF RESPONSE TO STANDARDIZED PEDIATRIC COLITIS THERAPY: A PROSPECTIVE MULTICENTER STUDY

Commentary on the original publication by Hyams et al. (Lancet 2019 [1])

By Prof. Emmanuel Mas
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Due to a lack of evidence-based data on therapeutic efficacy, there is uncertainty in the choice of treatment regimens in children who are newly diagnosed with ulcerative colitis (UC).

This is why the authors hypothesized that clinical, transcriptomic, and microbial factors prior to treatment could predict the course of the disease.

This inception cohort study recruited patients aged 4 to 17 years with newly diagnosed ulcerative colitis in 29 sites in the United States and Canada. Patients initially received mesalazine or corticosteroids with a pre-established protocol for escalation to immunomodulators (thiopurines) or biologic therapy with anti-TNFα. RNA sequencing was used to define rectal gene expression before treatment, and 16S sequencing to characterize rectal and fecal microbiota. The primary outcome was corticosteroid-free remission at week 52 with no therapy other than mesalazine.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

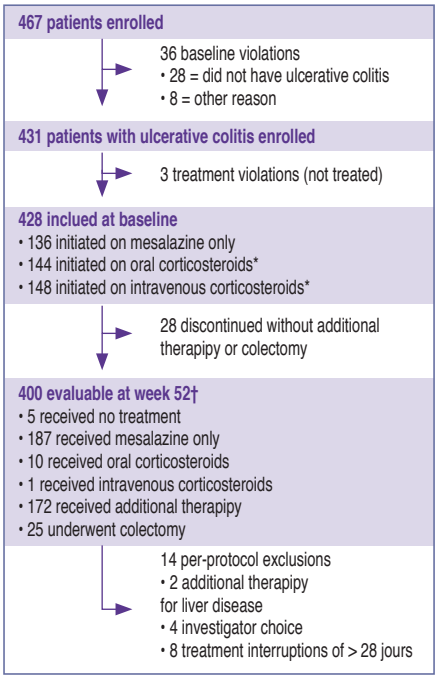
Clinical, biological and/or endoscopic scores such as the PUCAI (*pediatric ulcerative colitis activity index*), are used to classify the severity of pediatric UC. Disease severity can be scored as mild (PUCAI 10-30), moderate to severe (35-60) or severe/fulminant (≥ 65). 5-aminosalycilates may be effective in mild forms, while corticosteroids are used in moderate disease, although some children will become steroid-dependent or refractory and require escalation of therapy to immunomodulators or anti-TNFα. However, there is no prospective study evaluating the response to standardized therapy in newly diagnosed UC.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

Between 2012 and 2015, 467 children aged 4 to 17 years were recruited into this prospective multicenter study conducted in 29 sites in the United States and Canada (**Figure 1**). The primary outcome was week 52 remission, defined by a PUCAI score

▼ FIGURE 1

Study size



KEY POINTS

- The therapeutic decision depends on UC severity (PUCAI, Mayo scores) but also on treatment response by 4 weeks
- Other criteria (Hb, rectal eosinophil count, 25OH vitamin D) should also be taken into consideration
- Incorporating new parameters (gene expression and microbiota) into treatment decisions could facilitate the development of personalized medicine in the future

< 10, with no therapy other than mesalazine (no corticosteroids and no colectomy). Baseline severity was defined as mild (therapy with mesalazine or oral corticosteroids with PUCAI < 45), or moderate to severe (oral corticosteroids with PUCAI ≥ 45 or intravenous corticosteroids). In addition to the usual clinical and biological parameters, this study also assessed gene expression from rectal biopsies as well as the rectal and fecal microbiota before treatment.

428 children started therapy: mean age was 12.7 years, 50% female, 42% with mild disease (mean PUCAI 31.9 ± 12.1 SD) and 58% with moderate to severe disease (mean PUCAI 62.9 ± 13.2 SD). At week 52, 150 (38%) of 400 evaluable participants achieved corticosteroid-free remission, of whom 80 (49%) had mild disease and 70 (30%) had moderate to severe disease (**Table 1**).

▼ TABLE 1

Treatment response at 52 weeks

	Total (n=400)	Midle disease (n=163)	Moderate to severe disease (n=237)
Corticosteroid-free remission	150 (38%)	80 (49%)	70 (30%)
Immuno-modulators	74 (19%)	18 (11%)	56 (24%)
Anti-TNFα	123 (31%)	28 (17%)	95 (40%)
Colectomy	25 (6%)	2 (1%)	23 (10%)

The clinical, biological, and endoscopic parameters that were associated with corticosteroid-free remission were validated in an independent prospective cohort of 307 children. It should be noted that corticosteroid-free remission was achieved by week 16 for moderate to severe disease (after which it can no longer be achieved) whereas it could be obtained up to week 52 in mild forms. Moreover, even patients with very severe disease were able to achieve week 52 corticosteroid-free remission (41/133 [31%] with PUCAI ≥ 65) and, conversely, some patients with mild disease were receiving anti-TNFα at week 52 (13/90 [14%] with PUCAI < 35).

The authors identified 33 genes that were differently expressed between patients with moderate to severe disease who achieved corticosteroid-free remission (n = 51) or not (n = 101). Among these genes, 18 genes associated with cellular transport and ion channels were up-regulated and 15 genes involved in the antimicrobial response were down-regulated (**Figure 2**). The antimicrobial α-defensin signaling pathway showed the strongest negative correlation with week 52 corticosteroid-free remission. However, all 33 genes were negatively associated with the need for therapeutic escalation to anti-TNFα.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

It is important to keep in mind the predictors of corticosteroid-free remission and therapeutic escalation as determined from multivariate analyses.

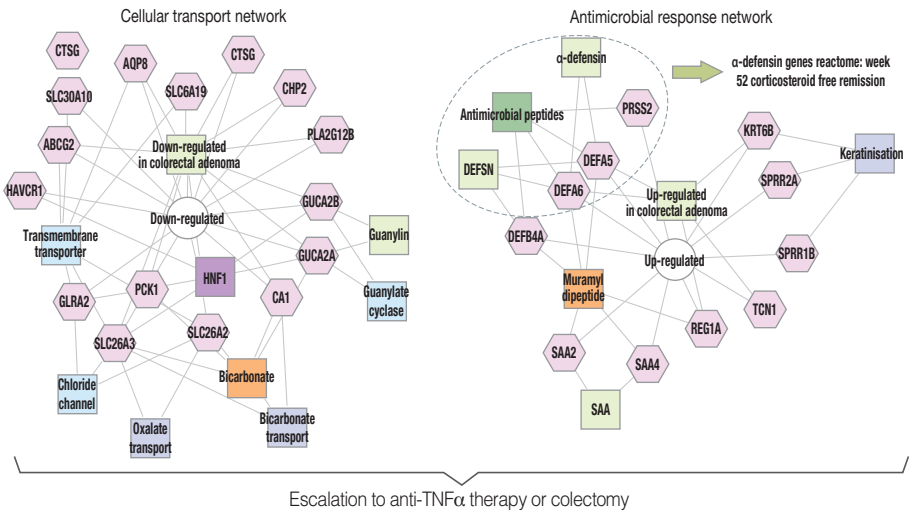
- Predictors of week 52 corticosteroid-free remission were:
  - PUCAI < 45, Hb ≥ 10 g/dL;
  - remission by 4 weeks;
  - low expression of antimicrobial genes;
  - increased relative abundance for Ruminococcaceae and decreased for *Sutterella*.
- Predictors of escalation to anti-TNFα therapy were:
  - total Mayo score ≥ 11;
  - eosinophil count in rectal biopsies < 32 per field at high magnification;
  - 25OH vitamin D < 20 ng/mL;
  - Hb < 10 g/dL;
  - no remission by 4 weeks;
  - decrease in genes involved in transport and antimicrobial genes;
  - decreased relative abundance of *Oscillospira*.

CONCLUSION

This study highlights the parameters that should be taken into consideration to guide the choice of therapy in children who are newly diagnosed with ulcerative colitis. Analysis of rectal gene expression and microbiota could both help predict the response to treatment and identify new therapeutic targets.

▼ FIGURE 2

Gene expression (RNA from rectal biopsies); genes are shown in hexagons and "functions" in squares



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NeuroGASTRO 2019

4th Biennial Meeting of the European Society of Neurogastroenterology and Motility and Postgraduate Course on Gastrointestinal Motility

September 5th to 7th, 2019
Centro Cultural de Belém Lisbon, Portugal

CONGRESS REVIEW

ESNM
European Society of Neurogastroenterology & Motility

By Prof. Fernando Man
Gastro Health,
Buenos Aires, Argentina

FOCUS ON THE 4TH BIENNIAL MEETING OF THE ESNM

SEPTEMBER 2019

LISBON, PORTUGAL

The 4th Biennial Meeting of the European Society of Neurogastroenterology and Moltility (Neurogastro 2019) was held from September 5th-7th in Lisbon, Portugal. More than 400 physicians and researchers from all over the world contributed to an oustanding meeting. Many late breaking investigational research and exciting conferences were presented.

IRRITABLE BOWEL SYNDROME AND MICROBIOTA

Irritable bowel syndrome (IBS) is a chronic disorder associated with pain and changes in fecal consistency and frequency of bowel habits. The influence of gut microbiota composition has been proposed as a target for study [1]. A decreased alpha-diversity with increased ratio Firmicutes/Bacteroidetes and increased *Streptococcus* and *Ruminococcus* has been described. Even though the treatment with probiotics in IBS is not ready for prime time, many studies have shown promising results. Small intestinal bacterial overgrowth (SIBO) has been associated with IBS in a subset of patients and lactulose/glucose breath test are used to diagnose SIBO.

During a Biocodex workshop entitled "Microbiome Based Strategies in IBS" Professor Magnus Simren emphasized that gut microbiota is altered in a subset of patients with IBS. An integrated framework of the pathophysiology of IBS has been proposed implying that the gut microbiota may interact with gut immune system, the epithelial barrier and the gut-brain axis. A specific gut microbial signature might be linked to IBS symptom severity. Also probiotics may produce changes in visceral hypersensitivity, neuromotor dysfunction, dysbiosis, disruption of the intestinal barrier and low grade inflammation. In fact, most meta-analyses favour the use of probiotics in IBS [2]. The problem remains in determining which probiotic is useful in each patient.

In a placebo controlled trial, *Bifidobacterium longum* (former *B. infantis*) has shown to be superior to placebo in the global assessment of symptom relief in IBS of all subtypes [3]. The proposed mechanism is a normalization of the balance of anti and pro-inflammatory cytokines Il-10 and Il-12.

The low FODMAP diet has been recently proposed. The long-term effect in microbiota composition and nutritional consequences deserve further studies. Responsiveness to a low FODMAP diet intervention may be predicted by fecal bacterial profiles.

Many exciting studies addressing IBS and microbiota were presented during the meeting.

Fecal microbial transplantation (FMT) has become a promising candidate in IBS treatment. However, a recent meta-analysis [4] showed no difference between placebo and FMT. The availability of a super-donor (healthy young athlete, 3 times-in-life antibiotic use) as shown in a study presented by M. El Salhy might be the key for better results.

In a poster presented by V. Passananti, *Bifidobacterium infantis* showed improvement in symptoms in non-responders to low FODMAP diet. The results were similar for severity and frequency of pain and abnormal distention. Also the number of severe cases of IBS was reduced by half. There was also a significant reduction of anxiety ($p < 0.005$) and depression ($p < 0.006$) scores.

The effect of a probiotic *Saccharomyces boulardii* (Sb) alone or multispecies (*Lactobacillus casei, L. rhamnosus, L. acidophilus, L. bulgaricus, Bifidobacterium longum* and *B. brevis*) was studied in 53 patients with bloating and abdominal pain and was presented by D. Vera in a study. Both probiotics showed a decrease in bloating and pain with a greater effect of Sb in abdominal pain relief ($p < 0.001$).

The impact of *Saccharomyces boulardii* (Sb) in IBS D with SIBO positive patients was evaluated by L. Bustos Fernandez. A trend to a greater decrease in breath test in Hydrogen excretion AUC from baseline in the Sb group was found in patients with an improvement of the IBS-SSS score and normalization of the Bristol Stool Scale as compared to control group. *Faecalibacterium prausnitzii* was more abundant coincidently with marked clinical improvement with Sb; stool consistency normalization (+ 120%), negative SIBO with improved IBS-related symptoms (+ 400%) and reduction of abdominal pain (- 76.5%). Mycobiota analyses showed significant modifications in Sb and phylogenic related lineage (*Saccharomyces* [+ 27%], *Debaryomyces* [– 88%]) and *Filobasidium* [> 1,000%]). In addition, the genus *Penicilium* and upper related lineage were 100 times more abundant in SIBO negative samples after Sb treatment.

MICROBIOTA AND OBESITY

The role of microbiota and obesity has gained great interest suggesting that certain microbiota signatures might increase the capacity of energy harvest.

P. Enck emphasized that a poor diversity in gut microbiota might also be used as a biomarker for obesity and that a specific microbiota signature drives individuals to prefer high caloric intake. The altered Firmicutes/Bacteroidetes ratio has been proposed as a condition but is this not specific to obesity. This has not been confirmed in recent meta-analysis [5].

In order to be relevant as a putative biomarker for obesity, the microbiota composition must be responsive to weight change, which is not always observed in bariatric surgery and conversely, changing the microbiota should induce weight change. Pre/probiotic nor FMT use have not accomplished with this aim.

Even though the gut microbiota is known to be involved in obesity, it not possible today to find a reliable signature as biomarker. Clinical trials in humans are interfered by daily nutrition and other factors such as probiotics, exercise and FMT.

MICROBIOTA AND BRAIN GUT AXIS

The gut microbiota plays a role in determining mental health and this has been targeted with the so called psychobiotics. The use of probiotics, prebiotics, diet, FMT and altering microbial consortia and metabolites represent an exciting field of investigation in stress-related disorders.

G. Clarke presented studies showing that the gut microbiota can modulate the amygdala volume and that a dendritic hypertrophy in basolateral amygdala neurons is observed in germ free animals. Serotonin and tryptophan, a serotonin precursor, play a role in the brain-gut microbiota axis. The microbiota can regulate the hippocampal serotoninergic system and tryptophan depletion normalizes depression-like behaviors. Also microbiota alteration is associated with stress induced despair behavior in rats and restoring the intestinal *Lactobacillus* levels normalized the stress induced behavior and ameliorated the serotonin production. A reduced microbial diversity is also present in depression with reduced *Prevotella*. Anhedonia-like behaviour, anxiety and tryptophan metabolism profile can be transferred via gut microbiota. The work presented by G. Clarke shows that *B. longum* could play an antidepressant role in rats and reduce stress response in healthy, healthy volunteers.

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CONGRESS REVIEW

By Prof. Patrick Bontems
Université Libre de Bruxelles, Brussels, Belgium

MAIN CONTRIBUTIONS ON INTESTINAL MICROBIOTA IN CHILDREN

JUNE 2019

GLASGOW, UNITED KINGDOM

ESPGHAN was created over 50 years ago and organises an annual congress attended by more than 4,000 participants coming from over 100 different countries.

DEVELOPMENT OF MICROBIOTA AT BIRTH

Exchanges between the mother and child determine the development of microbiota after birth. Any disruption to these exchanges increases the risk of developing certain disorders [1]. The main causes of dysbiosis induced during the neonatal period are caesarean birth, the use of antibiotics and the absence or premature discontinuation of maternal breastfeeding (before the age of 4-6 months). Given that some indications for a caesarean and a reasonable use of antibiotics cannot be called into question, the promotion of maternal breastfeeding remains a priority for paediatricians.

Several studies presented have strengthened this notion. For example, 267 children were monitored by Sakwinski *et al.* up to the age of two years. This longitudinal study showed that the risk of suffering a respiratory infection in non-breastfed infants was 3.84 times higher. The protective effect of breastfeeding is due to its modulation of the microbiota, since breast milk encourages the constitution of microbiota with a predominance of Bifidobacteria, as restated by Berger *et al.* The Berger study analysed stools collected from exclusively breastfed children in the United States, Belgium, Italy, Philippines and Bangladesh. The study showed that the predominance of Bifidobacteria was only present in 17% of infants in the United States, compared to an average of over 70% in other countries. This difference could be due to the composition of breast milk, to maternal microbiota, or to other environmental factors.

The composition of the microbiota of premature babies is disrupted following the separation of the mother and child. Administering breast milk can reduce such disruptions [2]. Thus, the oropharyngeal administration of colostrum stimulates the presence of Bifidobacteria, as shown by Feferbaum *et al.* In addition, the pasteurisation of colostrum results in an increase in Proteobacteria compared to raw colostrum. In a study conducted by Yamashiro *et al.* in Japan, the concomitant administration of colostrum and *Bifidobacterium breve* appeared to increase the colonisation of Bifidobacteria in the digestive tract and improve growth in premature babies.

HUMAN MILK OLIGOSACCHARIDES (HMO)

HMOs are the third component of breast milk [3]. HMOs are mainly galacto-oligosaccharides that have an effect on the microbiota [4]. In recent years, infant formulas have been supplemented with certain HMOs [5].

Many studies have been presented on this subject during the congress. For example, Binia *et al.* reported that the absence - due to a genetic variation - of 2'-fucosylated HMO in breast milk resulted in a higher frequency of respiratory infections. Sprenger *et al.* reported the findings of a controlled randomised study showing that this protective effect was due to the microbiota being richer in Bifidobacteria. Tomasi *et al.* studied the cognitive abilities of mice based on the presence or absence of 6'-sialyllactose. The memory and spatial orientation of mice improved when this HMO was present in the feed of young mice.

FAECAL TRANSPLANTATION

Faecal transplantation is a therapy used to modulate and restore/rebalance the microbiota of a recipient in cases of dysbiosis. The primary indication recognised at present is refractory or recurrent *Clostridium* colitis. A Chinese study conducted by Zhang *et al.* on 11 children reported a 64% efficacy after a single administration, with the other cases improving after 2-3 administrations. In another presentation, these same authors warned against the risk of such transplantations, especially in immunosuppressed patients. Adverse reactions were reported in 25% of patients - reactions that were particularly severe in two cases including one fatality.

SYMBIOSES

The development of symbioses probably offers a more reproducible solution for the future (no donor variation) and is potentially less dangerous than faecal transplantation. During the congress, the benefit of symbiosis was illustrated by a study conducted in Russia by Larkova *et al.* (food allergies) and by Lin *et al.* (non-alcoholic hepatic cirrhosis). In the latter study in mice, the authors demonstrated the protective effect of symbiosis in preventing fibrosis and steatosis in high-fat diets.

In addition, probiotics alone retain measurable clinical effects. During the congress, a controlled randomised trial versus a placebo arm conducted by Bastruk *et al.* highlighted the efficacy of *Lactobacillus rhamnosus GG* in improving the symptoms associated with cow's milk allergy. Nardi *et al.* restated the efficacy of certain probiotics in reducing the duration of acute gastroenteritis; Moretti *et al.* showed their effect in reducing the adverse digestive reactions of antibiotics, while Nocerino *et al.* reported their impact on functional digestive disorders in infants.

MICROBIOTA AND DIGESTIVE TRACT DISORDERS

Dyspepsia symptoms are very common and proton pump inhibitors often prescribed. Acharyva *et al.* showed that 60% of children with digestive symptoms suggestive of oesophageal or gastric conditions presented with intestinal fermentation (SIBO). The authors suggest that a glucose test should be performed in the event of a negative gastroscopy in such patients.

Several authors have highlighted the role of the microbiota in Crohn's disease, cystic fibrosis and lactose intolerance. However, a systematic review carried out by Bezawada *et al.* failed to demonstrate the role of the microbiota in autism. Equally, Lukasik was unable to demonstrate the link between the neonatal administration of antibiotics and autism.

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LITERATURE SELECTION

GUT MICROBIOTA AND AGE-RELATED FRAILTY

By Prof. Markku Voutilainen
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The authors have reviewed the role of gut microbiota and dysbiosis in the development of age-related frailty [1]. The physical manifestations of frailty are weight loss, muscle weakness, fatigue, sedendary lifestyle and slow gai. Muscle weakness is due to sarcopenia characterized by loss of both muscle mass and function, *e.g.* strength and power. The prevalence of sarcopenia is 5–13% and 11–50% in persons aged 60–70 and over 80 years, respectively.

Aging is characterized by increased inflammatory responses, endothelial dysfunction, changes of the immune system an increased nitrosative stress. With increasing age, the gut microbiome shows decreased biodiversity and increased number of pathogens. The changes are typical for persons aged over 65 years, and are attributable to altered diet composition caused by reduction in appetite, loss of dentition and chewing efficiency, swallowing disorders and malabsorption. Changes in microbiota are not uniform, but may be associated with geographical location, habitat, lifestyle (smoking, alcohol consumption), physical activity, the use of antibiotics and other medication as well as genetic factors. The most typical age-related microbiome changes are the diminution of butyrate-producing bacteria (Bifidobacteria, Firmicutes) and the increase of *Bacteroides*. There is a tendency to increasing number of opportunistic pathogens that may increase gut permeability. However, interindividual heterogeneity is wide.

Dysbiosis is associated with reduced muscle protein synthesis (anabolic resistance) leading to sarcopenia. The reduction of the short-chain fatty acids may have a central role in the disordered muscle energy and protein metabolism. Dysbiosis may also reduce the bioavailability of dietary amino acids and disturb vitamin metabolism of skeletal muscle cells. The main mechanisms of dysbiosis-induced sarcopenia are anabolic resistance, inflammation, disturbed mitochondrial metabolism, oxidative stress, and insulin resistance.

Deficient nutrition and physical inactivity have central role in the pathogenesis of sarcopenia and they also have major impact on gut microbiota. Conversely, gut dysbiosis may modulate systemic inflammation, muscle protein synthesis, insulin sensitivity and energy metabolism. At present, there is no evidence of specific microbiota composition of sarcopenic patients. The present review, however, supports the concept that gut microbiota mediates the effects of nutrition on muscle cells ("gut-muscle axis").

THE MEDITERRANEAN DIET, GUT MICROBIOTA AND NON-COMMUNICABLE DISEASES [2]

Mediterranean diet is characterized by high intake of vegetables, fruits, legumes, nuts, seeds, wholegrain cereals, moderate consumption of fish, and low intake of saturated fat, meat and dairy products with not more than moderate consumption of alcohol – in the first instance red wine. The diet of some people living in the Nordic countries resembles Mediterranean diet. People consuming Mediterranean diet have lower morbidity and mortality for cardiovascular diseases, and the diet has preventive and therapeutic effect on metabolic syndrome, obesity, type 2 diabetes, inflammatory diseases and some cancers.

Human gut is colonized by over thousand microbial species (bacteria, viruses, archaea, unicellular eukaryotic species) that contain over three million different genes (the human genome contains 23 000 genes). Microbiota ferments non-digestible dietary fibers and endogenous intestinal mucus which promotes the growth of microbes producing short-chain fatty acids (butyrate, propionate, acetate).

Dysbiosis is linked to localized inflammation of the gut mucosa, deterioration of gut physiology and metabolic disorders. Dysbiosis associates with many gastrointestinal and extraintestinal diseases. There is, however, significant interpersonal variation of the microbiota between persons with same disease and the microbial population is highly variable between different diseases.


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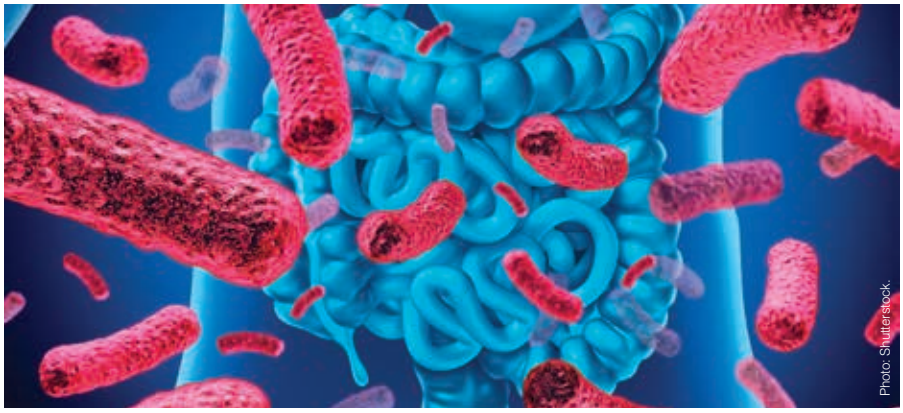
Animal studies have shown that diet has a strong effect on gut microbiome. Mediterranean diet contains complex carbohydrates which are fermented by healthy microbiota producing short chain fatty acids. Mediterranean diet has beneficial effects on microbiota and its metabolomic profile. Increased gut microbiota diversity has also been reported even after moderate intake of red wine. Mediterranean diet increases the abundance of *Bacteroides* and decreases Firmicutes. In persons with increased adherence to Mediterranean diet, the concentration of fecal butyrate and propionate is higher. A high Bifidobacteria/*Escherichia coli* ratio associates with good gut equilibrium and health is detected in persons adhering to the Mediterranean diet. This diet also increases levels of *Faecalibacterium prausnitzii* and certain clostridial species, and capacity of gut microbiota to metabolize food polyphenols.

Mediterranean diet has been suggested for the treatment of patients with metabolic diseases (type 2 diabetes, obesity, non-alcoholic fatty liver disease), because it may reverse dysbiosis and metabolomic profile disturbances often detected in these patients. However, more data are needed on the fluctuation and temporal patterns of gut microbiota in relation to the Mediterranean diet. We need also better understanding of the mechanisms by which diet modifies microbiota and how dysbiosis is involved in the pathogenesis of non-communicable diseases.

THE GUT MICROBIOME AND CHRONIC INFLAMMATORY DISEASES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The authors have reviewed gut microbiota alterations in chronic inflammatory diseases [3]. Chronic inflammatory bowel diseases (IBD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis/psoriatic arthritis (Ps/PsA) and systemic lupus erythematosus (SLE) are the major chronic immune-mediated diseases (IMID) affecting globally 5–8% of the population. Environmental stimuli initiate pathological immunological response in genetically susceptible individuals. Gut microbiome may start aberrant immune responses.

Ulcerative colitis and Crohn's disease are the two most common types of IBD in the western world, but their prevalence has increased globally. IBD is a chronic and incurable disease with low mortality most often diagnosed at a young age, which leads to compounding prevalence of IBD. IBD patients have an increased risk for other immune mediated diseases such as Ps, RA, AS and primary sclerosing cholangitis.

IBD patients have increased number of Proteobacteria (*e.g.*, adherent-invasive *Escherichia coli*), Pasteurellaceae, Veillonellaceae, *Fusobacterium* and *Rumincoccus gnavus*. IBD patients typically have lowered number of *Clostridium* groups IV and XIVa, *Bacteroides*, *Suterella, Roseburia, Bifidobacterium* and *Faecalibacterium prausnitzii*. Of the fungi, *Saccharomyces cerevisiae* is lowered. Of viruses, *Caudovirales* are higher in IBD patients.

Similarly to IBD, patients which multiple sclerosis have lower abundance of *Faecalibacterium* suggesting that this could be a sign of systemic inflammation. RA probably starts at the oral or gut mucosa and autoimmunity to citrullinated proteins is a typical phenomenon. Also in RA patients, a reduction of *Faecalibacterium* and increase in Actinobacteria was reported. We do not know whether gut dysbiosis is a cause or effect of RA. Of viral infections, parvovirus B 19 and hepatitis C are associated with increased RA risk. Also patients with AS, Ps/PsA, and SLE reportedly have altered gut microbiome profile.

In the gut, protective bacteria increase beneficial metabolites like butyrate and polysaccharide A stimulating regulatory T-cell production. Decreased abundance of these bacteria is typical for IMIDs leading diminished immune tolerance. Dysbiosis and increased gut permeability may stimulate dendritic cells at the gut mucosa resulting the production of inflammatory cytokines. Increase in xenobiotic metabolites (e.g. methane) stimulates TH 17 cells, which play important role in IMID pathogenesis. Stimulation of proteases may generate production of autoantigens typical for IMIDs. A decrease in butyrate-producing bacteria is typical for IBD and other IMIDs.

Long-term diet influences to gut microbiome profile, but also acute changes are detected. A change from animal-based diet to a plant-based diet alters gut microbiome within one day. The single diet components studied include animal, whey and pea protein, high/low fat, high saturated/unsaturated fat, lactose, artificial sweetener, fiber, resistant starch, probiotics and polyphenols. Mediterranean and vegetarian diet increase gut bacterial diversity, whereas western and gluten-free diet may decrease microbial diversity. Decreased bacterial diversity and loss of short-chain fatty acid producing bacteria are associated with IBD.

Dysbiosis profiles are common for IMIDs, but some dysbiosis subtypes are specific for single disease. Possibly a set of microbial metabolites produced by a variety of microbial compositions could be involved in the pathogenesis of IMIDs. Microbiome's functional profile may be the decisive factor in the IMID pathogenesis.

IBD, other IMIDs and metabolic diseases are associated with westernized lifestyle (diet, increased sanitation). Hygiene practices and the use of antibiotics may lead to unfavorable alterations of the microbiome, which could cause disorders in the maturation and function of the immune system. Probiotics and antibiotics are not effective treatments for IBD. Also only one third of ulcerative colitis patients reach remission after fecal microbial transplantation. The authors conclude that dysbiosis may not be specific for IBD but generally modulate the immune system. People may be genetically programmed to respond to immune changes in different organ systems leading to different IMIDs.

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