

THE GUT MICROBIOME, A POSSIBLE KEY TO MULTIDISCIPLINARY CLINICAL PRACTICE - LITERATURE REVIEW

Cristina Gabriela Schiopu¹, Radu Sebastian Gavrila¹, Cristinel Ștefănescu¹, Irina Mihaela Eșanu¹, Florin Mitu^{1,2}

¹University of Medicine and Pharmacy "Grigore T. Popa" Iași, Romania

²Academy of Medical Sciences of Romania

Corresponding author: Cristinel Ștefănescu

E-mail: cristinel.stefanescu@gmail.com

Abstract

Modern medicine tends to evolve towards interdisciplinary collaboration and case management. A strong example in that direction is represented by neurogastroenterology, a field that developed around the concept of gut-brain axis. Still, research in this field determines the multisystemic role of the gut microbiome, beyond its regulatory function within the gut-brain axis.

The purpose of this review is to focus on the current knowledge in medical literature regarding gut microbiome and its possible involvement in medical areas, such as cardiology, rheumatology, pneumology, neurology and psychiatry, bringing these domains closer than ever. We researched Google Scholar, Scopus, PubMed and Wiley Library for articles containing the following key words: "microbiota", "intestinal bacteria", "dysbiosis", "probiotics", "prebiotics", "rheumatology", "cardiology", "diabetes", "metabolic disease", "clinical medicine" "cardiology", "cardiovascular". Articles were selected by number of accesses, citations, results and by being published between 2015 and 2023. Both animal and clinical studies were considered as well as literature reviews and systematic reviews.

Although many studies are still in preclinical phase, and some of them still have uneven results, the road for research has contoured theories, especially regarding physiologic and pathophysiologic functions that involve the microbiome and have multisystemic consequences.

Conclusions. The gut microbiome may be the key of understanding multi-organic pathophysiologic mechanisms and may have the potential to act as a preventive clinical instrument and raising the effectiveness of therapeutic management in multiple medical fields, not only in gastroenterology and neuropsychiatry.

Keywords: microbiome, multidisciplinary, internal medicine, neuro-psychiatry, gut-brain axis.



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Rezumat

Medicina modernă tinde să evolueze și să promoveze tot mai mult abordarea și managementul interdisciplinar. Un exemplu în acest sens îl reprezintă neurogastroenterologia, care s-a dezvoltat pe baza cercetărilor privind axa intestin-creier. Odată cu studiile privind conexiunea dintre sistemul nervos central și mediul gastrointestinal, a devenit tot mai evident rolul microbiotei intestinale în modularea fiziologiei axei intestin-creier, iar ulterior a devenit tot mai clară implicarea acesteia în foarte multe dintre domeniile medicale.

Scopul acestui review este de a traversa cunoștințele actuale din literatura de specialitate în vederea argumentării importanței analizei microbiotei intestinale în domenii ca pneumologia, cardiologia, reumatologia, bolile metabolice, neurologia și psihiatria, aducând astfel valoare prevenției, dar și terapiilor aplicate în aceste specialități și promovând colaborarea interdisciplinară.

Am efectuat un review de literatură prin căutarea unei serii de cuvinte cheie, respectiv a combinațiilor dintre acestea, în bazele de date "Google Scholar", "Scopus", "PubMed", "Wiley Library", accesând articole originale respectiv articole de tip review de literatură și review sistematic, publicate în perioada 2015-2023. Cuvintele cheie utilizate au fost reprezentate de "axă intestin-creier", "microbiom", "floră intestinală", "disbioză", "probiotice", "prebiotice", "reumatologie", "medicină clinică", "diabet", "boli metabolice", "cardiologie", "cardiovascular", "pneumologie". Selecția articolelor a fost efectuată pe baza numărului de citări și accesări, a rezultatelor, atât studiile preclinice, cât și cele clinice fiind considerate relevante.

Deși foarte multe dintre studii se află încă în faza preclinică, iar unele prezintă încă rezultate neomogene, traseul cercetării este unul bine determinat, mai ales că mecanismele fiziologice și fiziopatologice în care este implicat microbiomul devin tot mai conturate, având un răsunet multisistemic.

Concluzii. Microbiota intestinală are funcții relevante sistemice, dincolo de reglarea dinamicii axei intestin-creier, în gastroenterologie și neuropsihiatrie, astfel încât poate avea un potențial atât preventiv, prin educarea pacienților și abordarea clinică timpurie, dar și un potențial terapeutic deosebit de important.

Cuvinte cheie: microbiotă, multidisciplinar, medicină internă, neuro-psihiatrie, axă intestin-creier.

Introduction

Hippocrates has left a historical statement that reverbs through time in the modern age of medicine. "All disease starts in the gut" is the phrase that nowadays tends to be more and more confirmed by all medical fields. Initially, in 1765, Scottish physician Robert Whytt describes "the nervous sympathy" as multiple nervous endings in the intestines that generated nervous energy throughout all internal organs. In the 19th century, the concept of "the great abdominal brain" develops though the general medical approach was to isolate each system and organ anatomically and functionally. The 20th century marks the beginning of the research of the connection between the gut and the brain, as clinical observations of functional gastrointestinal disorders and associated psychiatric symptoms become more evident. Through the research of the gut-brain axis, the gut microbiome becomes more and more relevant leading to major discoveries and constant evolution of the multilateral roles of the gut flora beginning with the 21st century. Although fecal transplant has been practiced in Chinese ancient medical practice and milk products were widely used for treating digestive symptoms, the foundation of these practices was not understood until modern medical research⁽¹⁾.

The intestinal environment and the gut-brain axis

The gastrointestinal tract represents an interface between external and internal environment and acts not only as digestive and metabolic function relay but also as an exchange and communication station. Clinical observations over functional digestive disease and inflammatory bowel

disease have revealed the bidirectional influence between the gut and the brain. The Central Nervous System (CNS) regulates the digestive function and homeostasis of the intestinal tract. It also modulates the enteroendocrine and enteric nervous system activity, the local immune responses and even the metabolic activity of some bacterial strains, such as *Lactobacillus*^(2,3).

The intestinal environment not only signals the brain about all functional and morphological alterations but also, it influences neurobiological function and alters the brain's activity, according to the latest research evidence. Animal and clinical model studies have demonstrated that association between neurotrophic, antidepressive and probiotic treatment does not improve memory and affective symptoms in vagotomised mice⁽⁴⁾. On the other hand, neurodegenerative symptoms may be improved by vagotomy and even the progression of the disease may be delayed with this procedure⁽⁵⁾. These studies are just examples from the multitude of clinical research results that prove the major bidirectional influence between the gut and the brain. Vagal connectivity is what generates the main bidirectional connectivity but the 2 relays are also supported by immunological, neuroendocrine activity and the circulatory system. As such, the gut-brain axis must be understood as an echo-system with constant dynamic interconnections and permanent physiologic and pathophysiologic influences between the CNS and the intestinal environment. Even if there is an apparent "health state", the underlying mechanism may be already disrupted and setting a long-term pathological trait⁽⁶⁾.

As research evolved, the mutual influence between the gut and the brain has been found to be regulated by a much more



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profound subsidiary mechanism that promotes the complexity of that influences. This mechanism is represented by the gut microbiome which can be viewed as a more of separate living and physiological entity that sets the basics of all systemic functions, not only the axis activity⁽⁷⁾.

Overview of the gut microbiome and its roles

The gut commensal bacteria consist mainly, in Firmicutes and Bacteroides fila with some additional fila like Actinobacteria, Fusobacteria, Cynobacteria, Proteobacteria and Verrucomicrobia. Lactobacillus, Bacillus and Bifidobacterium are most prevalent strains, followed by Akermansia, Sacharomyces, Streptococcus and Lactococcus. According to the Human Microbiome Project studies, the bacterial strains could carry more than 10 million genes that codify much more functions than the human genome could.⁽⁸⁾

The digestive and extra-digestive functions of the gut microbiome have been observed by 3 types of studies. The animal "germ-free gut" model has revealed the involvement of bacteria in metabolic, digestive and immune functions but also it proved the neuropsychiatric alterations compared to healthy controls. Also, this type of study allowed researchers to colonize the gut with specific bacterial strains in order to observe their

specific roles⁽⁹⁾. On the same study line, observations on antibiotics treatment in both animal and clinical studies, have revealed the development of digestive, neurologic, psychiatric and systemic dynamic symptoms development. In order to achieve efficient results and avoid antibiotic systemic adverse effects, the products administered had to act strictly in the enteric tract so the obvious choice was rifaximin and neomycin⁽¹⁰⁾. Finally, the most of clinical studies were conducted by observing the patient evolution while administering prebiotics, probiotics, and conducting fecal matter transplantation or observing post-vagotomy clinical evolution. This type of studies generated the relevance of preventive and therapeutic potential of the microbiome as not only digestive and neuropsychiatric improvement has been demonstrated, but also metabolic, immunologic and cardiovascular symptoms showed an improved prognosis⁽¹¹⁾.

The role of the microbiome begins with the digestive features and it's metabolic activities. The main characteristic of the gut bacteria is inhibiting pathogenic strain growth by competition. Onward, the digestive role expands through a multitude of traits: ramified amino acids synthesis such as valine and leucine that are necessary form external sources, can be synthesized by some bacterial strains. Carbohydrates and proteins are also metabolized by gut bacteria

and the synthesis, absorption and transport of minerals and vitamins are also a part of the microbiome's functions.⁽¹²⁾

The real important role of the microbiome and its involvement in the systemic homeostasis resides in the metabolism of carbohydrates that are the base of Short-Chained Fatty Acids (SCFA) synthesis. The SCFA are the structural and functional basic elements of multilateral physiological mechanism. Acetate, butyrate and propionate are the main SCFA produced by the enteric bacteria in healthy individuals and the specific roles of these SCFA echoes throughout the body in different ways⁽¹³⁾.

SCFA and immune responses

First of all, SCFA have major involvement in local inflammatory response and enteric immune activity.

This observation has been made by research in inflammatory bowel disease and especially on ulcerative colitis. Moreover, it seems that administration of SCFA forming bacteria, lowers the inflammatory response in the gut, by regulating the mucosal immune system. Butyrate has been associated with stronger modulation of CD4, CD45 T cells and inhibition of the pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF- α) and Interleukin 10 and 6 (IL-10, IL-6). It is believed that pathogenic bacterial production of lipopolysaccharides may trigger local immune response and induce cytokines activity with sustained inflammatory activity that will further have systemic impact⁽¹⁴⁾.

Also, autoimmune responses mediated by Immunoglobulin E (IgE), may be modulated by bacteria as several studies, show important elevation of serum IgE in germ-free mice when exposed to food antigens, compared to normal microbiota mice, where IgE remains at basal levels⁽¹⁵⁾. There is a

connection between some specific bacterial strains and the activity of histamine, as some studies suggest that *Lactobacillus reuteri* may have a role in histamine H2 receptor activity which may inhibit local inflammatory responses, although the results on this field are still uneven⁽¹⁶⁾.

SCFA and the nervous system

In terms of brain activity, its homeostasis is the most important for balanced function. It seems that SCFA may have an important role in mediating microglial activated neuroinflammation either by reaching the brain or by signaling through the gut-brain axis.

Present state of the art, suggests that, at least in animal models, microglial activity may be heavily triggered by pathogenic bacteria products such as lipopolysaccharides (LPS) and SCFA may have a role in reducing this inflammatory response. Both in vivo and in vitro animal model studies, suggest the same effect of SCFA by lowering inflammatory cytokines derived by microglial activation⁽¹⁷⁾.

Neurotransmitters are the foundation of CNS cognitive, behavior and affective processing. According to the recent studies, SCFA derived from gut bacteria metabolism, act as precursors for neurotransmitters and also use them to adjust signaling between the gut and the brain, via vagus nerve. Gamma-aminobutyric acid (GABA), dopamine (DA), serotonin (5-HT) are most present in dysbiosis studies, especially in those focusing on functional digestive disease with psychiatric symptoms association. It seems that probiotic therapy associated with antidepressants have much more potency in alleviating both digestive and psychiatric symptoms but also pain in the selected patients⁽¹⁸⁾.



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Cognitive deficits have been proved to improve significantly as probiotic therapy has been observed to promote the synthesis and activity of brain-derived neurotrophic factor (BDNF), N-methyl-D-aspartate receptor and neuropeptide Y system⁽¹⁹⁾. debates are still ongoing in the scientific community regarding the activity of neurotransmitters along the gut brain axis and the involvement of enteric nervous system in their activity and brain signaling and usage of these substances.

Dysbiosis and neuroendocrine activity

Dysbiosis is highly associated with a hyperactivity of the Hypothalamus-Pituitary-Adrenal axis (HPA axis) and especially with high levels of cortisol. Again, probiotic therapy has shown in animals model studies, to lower circulating cortisol and regulate HPA axis activity. The underlying mechanism is still uncertain but it is believed that due to the inflammatory local response in the enteric tract, cortisol levels begin to raise. Still, observations suggest that the HPA axis is further stimulated but offers no negative feed-back to control the cortisol levels. both inflammatory activity and high cortisol levels have been revealed during dysbiosis observations but with no Cushing-like effects and no negative-feedback to control those levels. This suggests that beyond regulating

the HPA axis and cortisol levels, the gut bacteria may be involved in corticoids receptor activity as probiotic administration normalize these functions. Still, more studies are needed in this area to fully understand the pathophysiological mechanism⁽²⁰⁾.

Metabolic activity and SCFA

As gut microbiome is specialized in carbohydrate metabolism, glucose homeostasis is a crucial target in diabetes studies. SCFA administration and probiotic therapy were both successful in improving glucose balance, maintaining normal glucose levels during anti-diabetic treatment and improving insulin sensitivity which suggest long-term preventive potential for negative outcome of diabetes and also improving efficiency of specific medication⁽²¹⁾.

Another study observed the levels of HbA1c and a jeun glucose levels after administration of high-fiber food. Butyrate levels in the fecal matter were elevated in an inverted proportional connection with a jeun glucose and HbA1c levels which may suggest that SCFA producing bacteria might have a therapeutic and preventive role in diabetes⁽²²⁾.

In obesity, research offers debatable results. If in glucose metabolism, SCFA levels in fecal matter prove to be useful in controlling glucose levels, there are studies that suggest

that the same high fecal matter SCFA may be associated with obesity, dysbiosis and cardiometabolic risk factors. Moreover, high SCFA excretion was associated with adiposity and cholesterol altered metabolism. Still, the fact that the excretion of SCFA was studied may raise the question if there is a misuse of SCFA during dysbiosis and there might be necessary to observe both circulating and excretion SCFA levels in these patients.⁽²³⁾

Weight loss is not very clearly associated with probiotic therapy but dietary weight loss is clearly impacting on the gut microbiome. In matter of dieting, the Mediterranean diet is being actively promoted as beneficial for gut bacteria diversity and has shown metabolic and cardio-vascular benefits. Other diets have shown inconsistent results in matter of gut microbiome and still need further reviews^(24,25).

Clinical evidence is nowadays preparing the medical practice for a new pathologic entity the needs both somatic and psychiatric attention. Food addiction is starting to become more prominent in medicine and has real chances to be soon recognized as an official diagnosis.

The problem with this pathology is the pathophysiology and the nature of the addiction. There is a strong debate in scientific community related to the nomenclature of the disease because some little evidence suggests addiction to food, other to eating behavior and some suggest both phenomena.

In matter of pathophysiology, studies reveal that the gut-brain axis and gut bacteria activity are mainly involved as satiety and hunger signaling through leptin, YY-peptide and ghrelin may be distorted in these cases^(26,27).

The mechanism is more complex as it involves stress processing, eating drive

maybe modulated by the reward system, dopamine disrupted activity, SCFA imbalance and the anorexic activity of glucagon-like peptide 1. All these disrupted mechanisms are altering the gut-brain system activity, affecting eating drive and craving and eating behavior. The involvement of gut microbiome consists in the fact that bacterial metabolites stimulate the endocrine enteric cells to release satiety hormones that promote secretion of leptin, insulin and ghrelin and modulate signals to the brain in order to regulate food intake and eating behavior, as well as other genetic factors which might influence metabolic activity⁽²⁸⁾.

Dysbiosis has been demonstrated to alter these mechanisms, alongside the affected serotonin activity, which may lead to pathologic eating disorder. Moreover, these observations, although they require stronger evidence, may have practical appliance in psychiatric eating disorders, if further knowledge will be added⁽²⁹⁾.

SCFA and intestinal wall permeability

SCFA production in the gut has a crucial structural role. And this role might hold the key to explain why microbiome balance or disruptions has systemic influence throughout the body.

SCFA are used for the synthesis and expression of tight-junction proteins such as claudines and occludins which hold a key role in maintaining the intestinal wall intact. They act as ligands to the G protein coupled receptors in order to hold the integrity of the intestinal wall and modulate the gut's permeability efficiently. Also, SCFA are used in mucus production by fermentation processes of specific carbohydrates, which holds another protective and barrier role^(30,31).



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Dysbiosis, leaky gut syndrome and the systemic consequences

Dysbiosis will not immediately affect digestive, brain and systemic functions but in time the integrity of intestinal wall and the enteric homeostasis will deteriorate as local inflammatory processes develop and commensal bacteria will be replaced with abnormal or pathogenic strain, exhausting the physiological mechanism and compensatory resources.

From bacterial community to the intestinal wall there are a series of elements that degrade as dysbiosis persists. Lack of commensal bacteria will deteriorate the mucin layer, sustained by caliciform cells and bacterial metabolism⁽³²⁾.

After that, inflammatory processes will "erode" the intestinal wall affecting enteroendocrine cells, immunity cells and secretion of anti-microbial and digestive substances, which hold also protective roles. Also, mechanical functions such as intestinal motility and peristaltic movement will also be disrupted as dysbiosis persist, because in the absence of bacterial physiologic metabolism, signaling to the brain will be distorted⁽³³⁾. As digestive stasis will take place, inflammatory activity, pathogenic bacteria metabolism and toxic accumulation of lipopolysaccharides and oxidative stress byproducts will accumulate in the gut with no efficient elimination

mechanism. As studies reveal, dysbiosis observed in majority of digestive diseases or even subclinical dysbiosis observed in animal models are associated with high levels of pro-inflammatory cytokines, especially TNF- α , IL-10, IL-6, toxic metabolic products, bacterial antigens, high levels of cortisol and free radicals, sustained by chronic inflammatory reaction. Furthermore, the eroding activity of the wall is completed by the lack of SCFA that affect tight-junction proteins⁽³⁴⁾. These proteins will run out and the integrity of the wall will be compromised increasing the intestinal permeability.

Scientific community refers to this phenomenon as "leaky gut syndrome" and it states the release of toxins, bacterial antigens and LPS, inflammatory cytokines and substances, free radicals into the blood stream⁽³⁵⁾.

This process will activate a chronic systemic inflammatory state as these products will continue to be present in the circulation and having the potential to affect any organ. After a period of time, the these circulating toxic byproducts will eventually exhaust the blood-brain barrier (BBB) filter function and the BBB permeability will be increased, allowing these substances, cells and antigens to invade the CNS and lead to neuro-inflammation and neuro-toxicity.

This will affect to top-down regulation and signaling system, inducing the body into a

vicious cycle of pathophysiologic mechanisms⁽³⁶⁾.

There are studies that actively demonstrated this feature. One study observed that adolescents with high anxiety and depression scores had also high circulating levels of permeability markers compared to control (zonuline and claudine-5)⁽³⁷⁾. Animal model studies have also shown that a germ-free gut is directly proportional associated with the grade of intestinal and BBB permeability. Moreover, administrating SCFA producing bacteria probiotics and fibers resulted in rehabilitation of gut and brain barrier integrity and improved digestive, affective and extra-digestive symptoms^(38,39). These studies bring arguments in favor of microbiota-related systemic and central nervous system alteration but also for the potential clinical therapeutical implications of probiotic and prebiotic therapy.

The leaky gut and respiratory diseases

As COVID 19 required fast, elaborated and efficient intervention, research had to focus on every aspect of the disease, bringing researchers together, worldwide, in a collective effort. As many patients presented both digestive and respiratory symptoms, questions about involvement of gut microbiota in the severity of COVID were raised.

Some studies focused on comparing influenza A virus and COVID virus influence on the gut microbiota and found that both viruses altered the bacterial diversity but in certain different ways. Interestingly, it seems that a lack of *Bacteroides* species were found in COVID patients, that have a negative regulation effect on the expression of ACE2 in murine models. Also, there is a notable inverted relationship between the abundance

of *Faecalibacterium* strains and COVID severity⁽⁴⁰⁾. Also, dysbiosis during COVID infection might not only allow the Coronavirus to bind to enteric ACE2 receptors but also cause a leaky gut that will enable it to circulate through the blood stream and affect other organs that express these receptors⁽⁴¹⁾. Chronic obstructive pulmonary disease (COPD) has been the focus for research related to gut microbiota. Although there are still discreet findings in this area, some studies suggest at least an indirect connection between leaky gut and the progression of COPD. Associated sarcopenia is a common finding in these cases and in small group observations, it seems that gut permeability marker zonulin has higher circulating levels compared to healthy control, together with free radical, inflammatory markers and especially reactive C-protein. Also, these findings were linked to muscle degradation in COPD patients. By far, the study suggests a possible linkage between dysbiosis, leaky gut and symptom severity in COPD⁽⁴²⁾.

Animal model studies were able to go further into research as interventional observations were available. As such, 16S rRNA sequencing and SCFA analysis of fecal matter in healthy controls and COPD patients were practiced. The COPD group was divided into GOLD scale I and II, III and IV respectively, for comparison purposes.

Fecal microbiota was transferred into 3 groups of mice and this procedure was repeated for 14 times in a total of 28 days. Previously to the transplantation of fecal matter, the mice were exposed to fuel burn smoke in order to induce COPD-like symptoms. At 28 days after inoculation and at 20 weeks, the mice's pulmonary function was analyzed. The COPD fecal matter receivers demonstrated severe deterioration in lung



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function, showing emphysematous lesions and hypersecretion of mucus, compared to receivers from healthy group. Also, gene sequencing demonstrated high differences in the bacterial strains and diversity of gut microbiome. *Prevotella* filia was more abundant in the COPD patient gut flora and also, a lower level of SCFA was found. These findings do not only suggest the linkage between dysbiosis, gut permeability and pulmonary diseases but also suggest a proportionality between dysbiosis and COPD progression⁽⁴³⁾.

The leaky gut and the autoimmune disease

In matter of digestive pathology, dysbiosis and related leaky gut are most certain related to autoimmune reactions, especially inflammatory bowel disease and food allergies. Inflammatory enteric processes are clearly a way leading to autoimmunity, as T and B cells get activated by both pathogenic bacteria and food antigens.

Also, zonulin is thought to be a precursor of haptoglobin 2 and it's release into the blood stream by tight-junction breakage in the intestinal wall, might be the cause for the pathophysiologic mechanisms involved in possible systemic autoimmune activity⁽⁴⁴⁾. Gut dysbiosis has been linked to autoimmune hepatitis, lupus and multiple sclerosis. In fact

one of the most spectacular studies focuses on multiple sclerosis patients and had interesting findings. The study transferred fecal matter from healthy people and multiple sclerosis patients into healthy mice. The multiple sclerosis fecal matter receivers developed spontaneous autoimmune encephalomyelitis.

CNS autoimmunity is a debatable subject in relationship with gut dysbiosis as scientific community still questions if the autoimmune response is linked to leaky gut, to the gut-brain axis or both⁽⁴⁵⁾. Most would say both as lupus and autoimmune hepatitis studies suggest the circulating autoimmune triggers to be involved in the pathophysiologic mechanism.

As glucose metabolism and the pathogenesis of type 2 diabetes are strongly related to gut dysbiosis, research tried to find if there are connections to type 2 Diabetes as well. Proofs in this direction are still uneven.

Although gut microbiota alterations have been found in clinical and animal model observations, there is still a question whereas the debut of type 1 Diabetes impacts the gut flora or it's the other way around. A fair observation stated that during the clinical evolution of type1 Diabetes, a leaky gut syndrome is associated with strong variations in post-prandial glucose⁽⁴⁶⁾.

One animal model study, observed that an elevated gut permeability, confirmed by high

zonulin levels, preceded the debut of diabetes with less than 30 days⁽⁴⁷⁾.

Gut dysbiosis and rheumatologic pathologies

Research in rheumatology is currently diving into gut microbiome subject and gut permeability related rheumatic pathogenesis. In fact, spondyloarthritis (SpA) and rheumatoid arthritis (RA) seem to have tight connections to gut flora balance, as studies show. More specific, the theory and observations, suggest that antigenic materials and immune cells travel through the blood stream when gut wall increases it's permeability and settles in the joints. Some results are still uneven as joint accumulation and eroding could be inconsistent and not homogenous and it might cause unspecified types of arthritis. In the same time, other studies suggest that the connection between dysbiosis and rheumatic diseases influence the progression of the pathologies and do not necessarily lead to the onset of symptoms⁽⁴⁸⁾.

Local intestinal zonulin related proteins were analyzed as well as circulating LPS binding protein and CD14 levels in patients with RA and the study concluded that colonic levels of zonulin were lower in association with high LPS binding protein and CD14 serum levels, compared to healthy controls.

This finding suggests that disease progression and clinical flare episodes might be influenced by gut increased permeability due to dysbiosis. ⁽⁴⁹⁾ gut diversity and SCFA producing strains abundance was also find to be different and rheumatologic disease compared to healthy controls.

As studies show, increased Clostridium, Eubacterium and Enterococci fila was found in the gut of RA and SpA patients while reduced number of Lactobacillus and Lactococcus was

observed in the same group⁽⁵⁰⁾. Rheumatic disease and gut microbiome associations still need more specific research in order to investigate whereas the potential of gut microbiome is strictly in a therapeutic direction or it could have preventive features.

Dysbiosis, leaky gut and cardiovascular disease

Systemic linkage between dysbiosis and cardiovascular risk and disease, have indirect and more direct approaches. As gut permeability increases and inflammatory markers and free radicals alongside antigens and toxic bacterial metabolites are released into the blood stream, in a long-term view, alterations to the vascular wall, systemic inflammation, hemoglobin deficits and platelet disfunctions might appear. Also, there are studies that suggest a cardiotoxic effect of pathogenic bacterial metabolites and free radicals as the cardiac muscle may increase it's oxygen need and usage and become exhausted⁽⁵¹⁾.

Metabolic disfunctions related to dysbiosis have to be taken into account as glucose and lipids metabolism are affected and the risk of obesity and diabetes increases. This will indirectly lead to cardiovascular risk because of hypertension, atherosclerosis, fatty liver disease associated with other metabolic diseases^(52,53).

A more direct approach of gut microbiome's implications in cardiovascular diseases emerged in the recent years and it focuses on the Trimethylamine N-oxide (TMAO) molecule. TMAO is an active molecule that inhibits cholesterol transportation to the liver, promoting dyslipidemia. In clinical practice, TMAO levels is directly related to atherosclerosis risk⁽⁵⁴⁾. Atherosclerosis is the result of a chronic inflammatory activity of



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endothelium but also of lipid peroxidative processes, leading to vascular stenosis with coronary stenosis having the most important cardiovascular risk.

The question in the matter is whereas TMAO promotes atherosclerosis only by altering lipid metabolism or it has some direct inflammatory effect on vascular endothelium. Also, some research suggests that TMAO might be involved in platelet activation and thrombus formation. the TMAO molecule is a bacterial product, more specifically, an amine oxide derived from trimethylamine oxidative processes and it is a bacterial metabolic product of L-carnitine and choline degradation.

Both choline and L-carnitine, can be found in high protein and high-fat foods and have their specific physiologic roles. So, the connection to the TMAO and the cardiovascular risk must be questioned in relation with abnormal elevated levels of TMAO and the possibility of pathogenic bacteria to increase the formation of TMAO during dysbiosis⁽⁵⁵⁾. In this direction some studies tried to associate dysbiosis with altered TMAO formation and the findings suggest that there are important differences between healthy controls and patients with TMAO and atherosclerosis. Moreover, *Proteus*, *Providencia* and *Escherichia* fila were found more abundant in these patients⁽⁵⁶⁾. Also, *Firmicutes* fila were more abundant than *Bacteroides* with

important absence of *Akkermansia* fila. In the same time, *Prevotella* fila and *Lactobacillus* *rhamnosus* were associated with low levels of TMAO⁽⁵⁷⁾. Still, the problem with these observations is the need for more specific studies as these strains might have associations not only to the cardiovascular risk but with other systemic features. it is commonly observed that one strain could be damaging or beneficial from a pathology to another, depending on it's abundance in the gut flora, so, in any type of study, attention to this possible bias should be taken into account.

Dysbiosis and chronic kidney disease

Similar to the cardiovascular risk associated with dysbiosis, TMAO might play a key role in the pathogenesis and progression of kidney disease. Animal model studies, have revealed that pure TMAO food supplementation induce progressive tubulointerstitial degradation and further renal failure. Clinical observations have also associated TMAO elevated levels to increased mortality risk in chronic kidney disease at 5 years follow-up. These findings suggest that gut microbiome could be a therapeutic and preventive target in kidney disease⁽⁵⁸⁾.

Other theories suggest that the leaky gut syndrome could be directly responsible for the onset and progression of kidney disease

as gut increased permeability might deliver uremic toxins or uremic-like substances into the blood stream along inflammatory markers and other toxic byproducts. According to this theory, there might be a double effect on the kidney, through a uremic and inflammatory pathway⁽⁵⁹⁾. The observations also suggest that dysbiosis and leaky gut could lead to short-term and long-term effects on the kidney as some studies reveal that acute kidney injury is also associated with dysbiosis⁽⁶⁰⁾.

Dysbiosis in neuropsychiatry and neuro-gastroenterology

Modern research validates multidisciplinary approach in medical practice and merging medical fields. Due to microbiome and gut-brain axis studies, gastroenterology is now more connected than ever to neurology and psychiatry.

As functional gastrointestinal disorders and inflammatory bowel disease are strongly associated to neurologic and psychiatric entities, it could be the time to recognize the interference of gastroenterology in all medical practice, in both preventive and therapeutical manners, targeting gut microbiota and dysbiosis as baseline for a large ambitus of pathologies.

In matter of connecting the gut and the brain, the double communication system, via vagus nerve and through the gut and BBB permeability appears to be the most important pathophysiologic aspect of brain injury and psychiatric symptoms. Moreover, due to the bidirectional nervous signaling between the 2 relays, a vicious cycle is often formed⁽⁶¹⁾. For example, in studies related to stroke and gut microbiome, results revealed that fecal matter transplantation might improve post-stroke recovery. On the other

hand, brain lesions altered the composition and diversity of gut microbiota. In other studies, dysbiosis or antibiotic treatment before stroke led to much more extensive brain lesions compared to healthy gut controls^(62,63,64).

Research in neurodegenerative diseases demonstrated a heavy preventive potential of gut healthy flora. Clinical observations have revealed that patient with inflammatory bowel disease have a higher risk of developing dementia compared to healthy controls and also, the age of the onset is lower⁽⁶⁵⁾.

Alzheimer disease might have even a stronger correlation with gut dysbiosis as it appears that amyloid-like peptides might be produced by pathogenic bacteria in the gut or, even the amyloid itself might be formed by *Escherichia* or *Shigella* strains. Further on, the leaky gut syndrome might be responsible for the amyloid peptides to reach the CNS when the BB barrier becomes hyper-permeable. Also, there are observations that oxidative stress resulted from leaky gut might accelerate the onset of Alzheimer disease^(66,67).

In Parkinson disease, both vagal and circulatory connections to the microbiome have been stated. Alpha-synuclein might be produced by certain bacterial strains such as *E. coli* or promoted by bacterial LPS but the propagation to CNS is highly debatable. Due to research on truncal and supra-selective vagotomy, there are evidence that this practice improves Parkinson symptoms and even stops the evolution of the disease^(68,69).

Psychiatry is maybe the most studied field in relation to the gut brain axis, especially because of functional gastrointestinal disorders that have opened the road for more profound observations. According to recent studies, psychiatry is not so far away from



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somatic alterations and some pathophysiologic mechanisms might promote systemic disruptions of dysbiosis and gut permeability.

More precise, affective disorders and anxiety are associated with high circulating inflammatory markers, especially TNF- α and IL-6 and free radicals^(70,71). The more interesting finding is that Selective Serotonin Reuptake Inhibitor antidepressants have a double anti-inflammatory and antioxidant effect. This finding promoted the development of the concept of psychobiotics which refers to therapeutic combination of antidepressants, prebiotics, probiotics and other mineral or vitamins⁽⁷²⁾.

Lactobacillus and *Bifidobacterium* strains are most used in this field as their impact on behavior, anxiety, mood and cognition seem to be most evident because of their role in the synthesis of serotonin, GABA and BDNF precursors and signaling.

These combinations could have therapeutical and preventive benefits in psychiatric and somatic associated pathologies, as their positive impact has been demonstrated in functional gastrointestinal disorders and inflammatory bowel diseases.⁽⁷³⁾ The anti-inflammatory and antioxidant effect of antidepressants on one side and the structural and functional benefits of probiotics, might have good impact even in other somatic disorders, at least as a

preventive method, especially because many organic pathologies evolve with some mood, anxiety or cognitive symptoms⁽⁷⁴⁾.

Discussions

It becomes more and more clear that the involvement of gut microbiome in general health and disease reaches far more relays than the gut-brain axis. Indirectly or more directly, the microbiome is a living entity inside "the great abdominal brain" that seems to function as a driving tool for physiologic and pathophysiologic mechanisms and in some cases, dysbiosis activates a "domino-like cascade" of reactions that initiate and promote systemic imbalances. The clinical approach of the microbiome, from any medical field, needs to follow general and specific anamnestic steps in order to understand whether or not, the gut microbiome might be a subsidiary problem in the case. An extended review of the gut-brain axis is proposing some characteristics that could be used as a general algorithm in clinical practice when investigating possible microbiome related features.

First of all, by indistinguishability is one of the present characteristics. The microbiome acts like a superorganism in an interdependent relation to our body and specific individual traits of bacteria are still unavailable⁽⁷⁵⁾. By emergence, the concept refers to the

Bacterial strain	Digestive/possible systemic effect	Neuropsychiatric effects
<u>Lactobacillus casei</u> ⁽⁷⁸⁾	Anti inflammatory, pain sensitivity	Mood, anxiety, behavior
<u>Lactobacillus plantarum</u> ⁽⁷⁹⁾	Anti-inflammatory	Expression of BDNF ¹ →cognition
<u>Lactobacillus acidophilus</u> ⁽⁸⁰⁾	Pain modulation	Potential role in cannabinoid receptor activity
<u>Lactobacillus brevis/rhamnosus/reuteri</u> ⁽⁸¹⁾	Anti-inflammatory, SCFA ² production, gut permeability	Sleep, mood, anxiety → high impact on GABA ³ and serotonin
<u>Bifidobacterium longum/lactis/breve</u> ^(82,83)	Pain sensitivity, SCFA ² production, gut permeability	Mood, anxiety, stress Possible anti-neurodegenerative role Suggested utility in autism/AD/HD ⁴
<u>Genul Bacillus (subtilis)</u> ⁽⁸⁴⁾	Antioxidative, anti-inflammatory, pain sensitivity	Cognition, mood, behavior
<u>Saccharomyces (boulardi, cerevisae)</u> ⁽⁸⁵⁾	Antioxidative, anti-inflammatory	Cognition, mood
<u>Genul Akkermansia</u> ⁽⁸⁶⁾	immune cell regulation, gut permeability	Gognition, anxiety
<u>Lactococcus</u> ⁽⁸⁷⁾	Anti inflammatory (especially in IBD ⁵)	dopamine activity, mood, behavior
<u>BACTEROIDES</u> ^(88,89) <u>Clostridium butyricum</u>	Anti-inflammatory, gut permeability	Anti-neurodegenerative role Cognition/behavior → suggested in autism/AD/HD ⁴
<u>FIRMICUTES/BACTEROIDES</u> ⁽⁹⁰⁾	16S rARN sequencing→suggested normal F/B = 16-620 (Genova Diagnostics) → different results in different pathologic traits.	
1- rain derived neurotrophic factor 2- hort chain fatty acids; 3- amma-amynobutiric acid;	B 5- Attention deficit/hyperactivity disorder 6- Inflammatory bowel disease	

Table 1. Specific bacterial strains suggested to have beneficial effects, if used as probiotics



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pathologic meaning of not only the absence of the commensal bacteria but also the changes in their diversity and functions which could lead to the same negative effects. The bidirectional signaling path between the gut and the brain has multiple associated functional traits like circulation, neuroendocrine, immune system and other elements of the nervous system. This is one of the reasons, the microbiome has such a great influence throughout the body.⁽⁷⁶⁾ By the dynamic of critical periods, the patient's developmental history might have an important setting for the balance and health of the microbiome.

As studies show, peri/post-partum periods and childhood gut dysbiosis might set the adult life gut bacterial balance aside from the fact that gut bacteria change in composition through every age period and with every influence from the external environment (diet, drugs). As such, we might find prognostic factors for some pathologies. For example, weak bacterial colonization or gut infections during childhood appear to be involved in the pathophysiology of autism spectrum disorder⁽⁷⁷⁾.

Finally, the homeostasis of gut microbiome and gut environment must be analyzed from all functional and structural perspectives. The lack of knowledge about specific bacteria related to systemic diseases is still a problem for the clinical practice but research in the

matter of gut-brain axis have revealed some suggestive directions towards concrete association between gut flora and somatic disorders (Table 1).

Conclusions

As medicine evolves toward interdisciplinary collaboration and many medical fields tend to merge in some directions, the gut microbiome tends to be one of the fundamental pillars of health and disease, as its influences reach multiple aspects of systemic pathophysiologic mechanisms. Although the research is abundant, many areas need furthermore understanding and even more important, observations from animal model studies need to pass clinical validation.

Specificity in term of gut bacteria and their active roles throughout the body needs completion because many bacterial filaments have both beneficial and negative effects and quantitative and qualitative aspects of bacterial diversity must be taken into consideration when gene sequencing might be a current diagnostic instrument. Still, the course for research and clinical practice in the field of the microbiome is full of potential for preventive medicine as well as for therapeutic approach and multidisciplinary management of diseases and maybe in the future, public health and education might

include the knowledge about the microbiome in it's spectrum of appliance.

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