

Impact Of Human Aging And Modern Lifestyle On Microbiota

Maria Gabriela Valle Gottlieb^{1*}, Vera Elizabeth Closs², Vilma Maria Junges³, Carla Helena Augustin Schwanke⁴

¹Biomedical Gerontology Graduate Program, Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul (IGG-PUCRS), Av. Ipiranga, 6681-703, CEP: 90619-900, Porto Alegre - RS -- Brazil. E-mail: maria.gottlieb@pucrs.br

²Biomedical Gerontology Graduate Program, Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul (IGG-PUCRS), Av. Ipiranga, 6681-703, CEP: 90619-900, Porto Alegre - RS -- Brazil. E-mail: veraec@terra.com.br

³Biomedical Gerontology Graduate Program, Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul (IGG-PUCRS), Av. Ipiranga, 6681-703, CEP: 90619-900, Porto Alegre - RS -- Brazil. E-mail: vjungesnutri@yahoo.com.br

⁴Biomedical Gerontology Graduate Program, Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul (IGG-PUCRS), Av. Ipiranga, 6681-703, CEP: 90619-900, Porto Alegre - RS -- Brazil. E-mail: schwanke@pucrs.br

***Corresponding author:** Maria Gabriela Valle Gottlieb, Biomedical Gerontology Graduate Program of the Institute of Geriatrics and Gerontology, Pontifical Catholic University of Rio Grande do Sul (IGG-PUCRS), Av. Ipiranga, 6681-703, CEP: 90619-900, Porto Alegre - RS -- Brazil, E-mail: maria.gottlieb@pucrs.br, Phone: +55-51-33368153/FAX: +55-51-33203862

ABSTRACT

Human evolution and lifestyle changes caused by the agricultural and industrial revolutions have led to great advances in medicine and increased life expectancy, whilst also profoundly altering

the ecological relationships and disease patterns of populations. Studies involving populations that still enjoy a rural way of life and with traits similar to the Paleolithic period reveal them to present a more robust, resistant and diverse gut microbiota, in comparison to highly industrialized civilizations. The human diet has expanded and broadened to include the consumption of high-calorie foods, particularly from animal sources such as game, meat and eggs. For some time, the authors have been alert to the fact that a modern lifestyle leads to reduced intake of beneficial bacteria, suggesting that nonpathogenic bacteria are being eradicated. Furthermore, therapeutic procedures, including the use of probiotics and prebiotics, have been proposed to lead to recovery of this microbiota, which is altered due to both the ageing process and lifestyle related aspects. Accordingly, this article aims to review the impact of human aging and modern lifestyle on gut microbiota, within an evolutionary, ecological, epidemiological and therapeutic context.

Keywords

Microbiota, probiotics, prebiotics, aging, lifestyle, evolution.

INTRODUCTION

Evolution of Human Aging and Lifestyle

The aging process is universal, progressive, gradual and inexorable (Troen, 2003). According to some authors, aging is a degenerative and time-dependent process, which affects many organ systems at different rates. Moreover, it is often associated with functional and fertility/fecundity decline, as well as increased susceptibility to chronic noncommunicable diseases and death (Kirkwood and Austad, 2000; Finch, 2007).

The aging population phenomenon is a recent condition in human evolutionary history. The *Homo* genus emerged on Earth around one to two millions years ago and *H. sapiens* appeared in the last 190,000 to 200,000 years. It is important to highlight that 98% of human existence transpired in the Paleolithic period (2 million to 10,000 years BC) (Dalgarrondo, 2011). Paleoanthropology studies suggest that in this vast period of existence, the life expectancy of the *Homo* genus was relatively low at around 19-20 years of age and remained low until the 18th century (~25 years) (Lancaster, 1990). A research published in 1842 reported the presence of only 16 centenarians (maximum lifespan of 111 years) in January 1831 in Belgium (Quetelet, 1842). Although centenarians or the super-long-lived elderly are a physiologically distinct group, it is perhaps important to highlight that this characteristic has always existed among populations, albeit in restricted numbers, and that more latterly, it has been gradually increasing (Meyer, 2010). However, what are the intrinsic and extrinsic factors that have been responsible for the increase in longevity and aging of the population in the last two centuries of evolutionary history? The agricultural and industrial revolutions are known to have caused major sociodemographic, economic, cultural, epidemiological and ecological transformations in the

lives of individuals, including increased longevity. In relation to epidemiological and ecological changes, the evidence confirms that *H. sapiens* during the Paleolithic period lived as nomadic hunter/gatherers, feeding mainly on fruits, tubers, roots, seeds, crustaceans and mollusks, suggesting a negative energy balance (Armelagos et al., 2005). Furthermore, studies suggest that disease patterns in the Paleolithic period consisted mainly of infectious and parasitic diseases. According to Sprent (1962), parasites affecting the paleo-hominids were inherited from anthropoid hominid ancestors, and remained coexistent after speciation occurred. The most prevalent species of human parasites during this period, including bacteria, are believed to have been the *Pediculus humanus*, *Phthirus pubis*, *Salmonella typhi*, *Staphylococci*, *Trypanosoma sp*, *Schistosoma sp*, *Clostridium tetani* and *Trichinella sp*, among others (Cockburn, 1967). In addition, the environment could create discrepancies in the rates of infection and gender-dependent mortality, due to gender-based differences in activities (women were mainly gatherers and men hunters) (Armelagos et al., 2005).

The Neolithic period (10,000 BC to 4,000 BC) Agricultural Revolution demarcated the domination of man over food production, animal domestication and the establishment of lands and housing (sedentary lifestyle). This lifestyle and agricultural production quickly led to the accumulation of food surpluses, which promoted important changes in human society (Armelagos et al., 2005).

The rapid increase in population and population density, sedentary lifestyle, animal domestication, the extensive breakdown in ecological balance (territory occupation for monocropping food and insertion of exotic species), and the emergence of social inequality were all factors that increased the risk of infectious diseases in the Neolithic populations (Armelagos

et al., 2005). In addition, physical inactivity increased parasitic infections due to the proximity between water resources and the disposal of human and domesticated animal waste, which jointly created a favorable environment for disease vectors (Hoberg et al., 2000). Coupled with a sedentary lifestyle, subsistence agriculture increased nutritional deficiencies with major implications for the health of populations. Subsistence agriculture decreased the variety of foods available to individuals, reducing the dietary niche, which may have resulted in increased vulnerability to infectious diseases and the appearance of chronic noncommunicable diseases due to the loss of diversity of the gut microbiota. Therefore, the human diet, including energy intake and energy expenditure, began to change over the last 10,000 years in line with a gradual increase in longevity, with the biggest change happening in the last 150 years with the advent of industrialization (Eaton and Konner, 1985; Simopoulos, 1999). With increasing life expectancy, there was greater exposure to the aging process and the morphophysiological and ecological modifications (microbiome and microbiota) that it caused.

The last 10,000 years have been characterized by major changes in the diet and lifestyle of the *H. sapien* species. Faced with this new *modus operandi*, several positive adaptations and physiological gains have occurred, such as increased longevity, but also harmful effects on the gut microbiota.

In this sense, the aim of this paper was to perform a narrative review of the literature related to the impact of aging and modern lifestyle on gut microbiota, within an evolutionary, ecological and epidemiological context.

Impact of aging and modern lifestyle on the gastrointestinal tract (GIT) and microbiota

The last century in the evolution of demographic aging has seen a great change in world life expectancy, with growth in the number of elderly people (United Nations, 2013). In this context, it is known that a healthy nutrition is an important factor in quality of life, although there is no evidence that having an adequate nutritional status contributes to increase the human life cycle (Harris, 2013). Improvements in modern medicine and an awareness of healthy lifestyle practices may potentially lead people to experience longer lives and, in general, healthier lives than their ancestors (Lynch et al., 2015).

A part of the developing world, however, continues to have insufficient availability of safe food and nutrients, and these difficulties are caused more by wars and other political events than natural situations. It is also true that where an abundance and variety of food is the case, such as in wealthier countries, health problems arise from excessive consumption and a sedentary lifestyle. The caloric expenditure required for manual labor has decreased dramatically but, nonetheless, people have maintained the usual eating habits. A healthy diet is not enough to improve health if it is not accompanied by daily physical exercise. Replacement of the physical effort that formed part of almost all jobs in the past is necessary (Fara, 2015).

Appropriate nutrition is also associated with the capacity of food to preserve cultural aspects of the population, like conviviality and the sharing of food, which are considered good mechanisms for socialization and the improvement of family and community lives (Fara, 2015).

Each individual also has their own specific biochemical needs that are affected by the modern lifestyle, with consumption of chemical products, inadequate procedures for food storage and distribution, excessive use of refined foods, cooking methods, excessive consumption of fried foods, drugs and medications, and environmental pollution. All these factors can lead to

organic imbalance, especially in microbiota, and to the emergence of diseases (Milan and Cameron-Smith, 2015). The majority of people nowadays consume foods produced and prepared by others. There is a dependence on commercial chain suppliers that produce, transport and sell to consumers who are far from the place of origin of the foods, and bacterial contamination of food products are common, together with the presence of pesticides and preservatives (Schell et al., 2012).

Yet despite the importance of nutrition, relatively little is known regarding the impact of advancing age on gastrointestinal function, digestive reactions and the metabolic adaptations that occur in response to ingested food (Milan and Cameron-Smith, 2015). The gastrointestinal tract is a complex system and its diverse cells perform a series of functions essential to life, such as secretion, digestion, absorption and defense. Physiological age-related alterations are common and an inherent part of the cell aging process, but they also vary and can be influenced by external factors (Saffrey, 2013).

The elderly may also present changes in motility of the oropharyngeal muscles and in swallowing, gastroesophageal reflux, and diminished gastric motility and emptying; decreased gastric (acid, pepsin) and pancreatic exocrine secretions, dyspepsia, irritable bowel syndrome, constipation, indigestion and reduced absorption of nutrients, all of which can lead to malnutrition (Grassi et al., 2011). Physiological changes can lead to inadequate nutrition and micronutrient deficiencies, which, in turn, are associated with changes in microbiota and decline in organ function. This can result in a higher risk of infections and chronic diseases (Biagi et al., 2012).

Other non-physiological factors that feature as part of a modern lifestyle can also contribute to the impact associated with aging of the gastrointestinal tract, such as: inadequate intake of water, calories and nutrients; difficulty in food preparation; psychological factors, including depression; and social factors like isolation and low-income (Quercia et al., 2014).

Age-related alterations in gut physiology have an important effect on the diversity, composition and functional characteristics of gut microbiota (Konturek et al., 2015). The microbiota undergoes an evolutionary trajectory over the course of human life and has the structural and functional layout of its ecosystem modified from infancy to old age, providing the host with finely calibrated ecosystem services for each stage of life (Quercia et al., 2014). Studies have suggested that the loss of diversity and increase in pathogenic microbiota may be linked to the inflammatory process associated with aging and diseases, including cachexia, frailty, *Clostridium difficile* colitis, atherosclerosis, vulvovaginal atrophy, cancer, and metabolic and neurological diseases (Konturek et al., 2015; Bischoff, 2016). Moreover, changes in gut microbiota may increase the permeability of the intestinal barrier, increasing the risk of developing chronic diseases (Konturek et al., 2015).

The human body can be considered a complex and diverse ecosystem, given the enormous variety of microorganisms that dwell within. It is inhabited by 100 trillion microbial cells (10 times the number of body cells) and hosts over 1000 different species, with a metabiome 150 times larger than our own genome, which assists in modulation of our genetic and metabolic regulation (Gill et al., 2006).

The microorganism interactions established in the small intestine of a host are relationships of symbiosis, commensalism and parasitism, and are associated with the ability of

microorganisms to metabolize compounds that would not be metabolized if microbes were not present. These interactions depend on the food type of the host, whether they be an omnivore, herbivore or carnivore (Ley et al., 2008). Eating habits are, therefore, one of the most important factors for the diversity of our microbiota.

Participation of microbiota in the human digestive system is essential, as the epithelium of the GIT is adapted to the absorption of simple molecules, such as glucose and short-chain organic acids, and microorganisms play an important role in the conversion of polysaccharides into products that can be absorbed by the epithelium (Machado et al., 2015). One of the benefits the host obtains from its ecological and, in general, harmonious relationship with the microbiota is the antagonism that occurs between some microorganisms and pathogen populations. That is to say, the inhibition of pathogenic microorganisms can occur by the production of antimicrobial compounds and competition for nutrients and/or adhesion sites, to the advantage of those that are non-pathogenic (Machado et al., 2015).

Among its functions, microbiota supplies a source of energy, nutrition and health maintenance for the host (Lakshminarayanan et al., 2014). Healthy microbiota is able to defend the host organism against the invasion of harmful micro-organisms, and also has an important role in preserving the integrity of intestinal walls, innate immunity, insulin sensitivity, metabolism and in crosstalk with brain functions (Halmos and Suba, 2016). Imbalance between the microbiota and host leads to dysbiosis, which, in turn, contributes to the installation of an inflammatory process and negatively affects glucose metabolism, insulin resistance and obesity, while increasing the risk for development of metabolic syndrome, type II diabetes, inflammatory bowel diseases, autoimmune diseases and cancers (Halmos and Suba, 2016). The relationship

between the host and alterations in the composition of their gut microbiota is associated with disease progression, as well as with frailty in the elderly population (Pérez-Martinez et al., 2014). Many factors influence the host microbiota, from the maternal microbiome and type of delivery, to genetic aspects, hygiene, hormonal status, diet, exercise, medications used, body weight, location, circadian cycle and, especially, the age of the host (Sekirov et al., 2010; Halmos e Suba, 2016).

Desbonnet et al. (2015) showed that the use of antibiotics causes depletion and restructuring of the gut microbiota, reduces anxiety but induces cognitive deficit, alters the dynamics of the tryptophan metabolic pathway, and significantly decreases brain-derived neurotrophic factor (BDNF) and expression of oxytocin and vasopressin in the brain in mice. These findings strongly suggest there is a relationship between gut microbiota and neuromodulation and neurotransmission, and that environmental factors, such as medications and their excipients, can interfere with this harmonious relationship, contributing to the pathogenesis of psychiatric disorders like depression.

It is important to highlight that the elderly, in general, experience polypharmacy (defined as the use of multiple drugs, commonly five or more) due to the occurrence of multiple morbidities that affect them. The number of medications, complexity of treatment regimens, especially in the presence of comorbidities, and pharmacokinetic and pharmacodynamic changes inherent to the aging process are factors that increase the vulnerability of this age group to adverse events, either by reactions to medications or medication interactions that can cause damage, primarily to the microbiota (Rozenfeld et al., 2008).

Studies have shown that an inter-individual variability exists in relation to changes in the elderly's microbiota, pointing to other causes beyond aging (Pérez-Martinez et al., 2014) and the use of medications (Lakshminarayanan et al., 2014), which are associated with other important factors, such as diet and lifestyle (Pérez-Martinez et al., 2014).

Some dietary changes linked to aging and which are associated with modification in the microbiota may occur due to the lack of mechanical oral function, diet preferences and appetite. These alterations could result in increased consumption of low-nutrient dense and high fat/sugar content foods, as well as a reduction in consumption of food of vegetable origin (Claesson et al., 2012).

At this stage of life, microbiota composition may also be related to distinct dietary patterns, governed by where the elderly are living, more specifically, whether they are living at home, in places for rehabilitation, or in long-term care facilities (Claesson et al., 2012; O'connor et al., 2014).

Researches has shown that changes in diet and increased frailty in the elderly accounts for differences between the microbial quality and diversity of individuals living in long-term care institutions and those living in the community (Claesson et al., 2012; Lakshminarayanan et al., 2013)

For some time, authors have been alert to the fact that a modern lifestyle leads to a reduced intake of beneficial bacteria, suggesting that nonpathogenic bacteria are being eradicated (Cedgard and Widell, 2001).

Therapeutic procedures have been proposed for restoration of the microbiota that has been altered due to both the aging process and lifestyle aspects, among them the use of probiotics and prebiotics (Halmos and Suba, 2016).

Impact of lifestyle, probiotics, prebiotics and symbiotics on microbiota

It has been known for decades that probiotics (living microorganisms) when properly administered confer a beneficial effect on the health of the host (Hill et al., 2014). They have also been used in different food products and diets due to their positive effects in health promotion (Machado et al., 2015). The actions of probiotics are interrelated and beneficial, aiding in the fermentation of complex carbohydrates and their absorption by the GIT. Probiotics help in the provision of essential vitamins, especially the B group and vitamin K. They also compete with pathogenic microorganisms in the gastrointestinal tract like antagonists and intestinal pathogenic neutralizing agents; metabolizing and neutralizing carcinogens present in food; and positively modulating the host's immune response to infection and disease (Nogueira, 2011).

Another well-established scientific fact refers to the benefits of prebiotics, food that is no digestible by the host, which stimulates bacterial growth and activity from its fermentation in the colon (Ferreira and Silva, 2010). Prebiotics also promote selective stimulation of growth and activity of one or a limited number of microbial species that provide health benefits for the intestinal environment (Roberfroid et al., 2010). The desired relationship between the population of microorganisms and their host is normobiosis, which is the key to good health and wellbeing (Roberfroid et al., 2010). Dietary-based strategies aimed at homeostasis of the intestinal microbial ecosystem (probiosis and prebiosis) to promote host health (Conlon and Bird, 2015)

have been associated with the maintenance of elderly health and with the hypothesis that it would impact on the longevity of the host (Claesson et al., 2012).

Potential probiotic species can be classified into two distinct groups: the lactic acid bacteria (*Bifidobacterium*, *Lactococcus*, *Lactobacillus*, *Leuconostoc*, *Pediococcus*, *Oenococcus oeni*, and *Streptococcus thermophilus*) and other probiotic species (Lutgendorff et al., 2008). The most studied microorganisms are *Bifidobacterium*, *Lactobacillus* and *Streptococcus*, as well as yeasts, such as *Saccharomyces boulardii* (Martinez et al., 2015). Among the essential prebiotics there are insulin-type fructans and fructo-oligosaccharides (FOS) occurring naturally in plant products (bananas, garlic, onions, wheat) (Sabater-Molina et al., 2009); and galacto-oligosaccharides (GOS), formed from lactose-rich substrates rich in lactose (Cavalcante Fai and Maria Pastore, 2015). The bacterial target groups of the prebiotics are typically the *Bifidobacterium* and *Lactobacillus* (Conlon and Bird, 2015).

Probiotics have been used in the prevention and treatment of diseases, such as allergies, gastrointestinal and urogenital infections, inflammatory diseases, cystic fibrosis, and certain types of cancer, among others (Nogueira, 2011). The benefits of probiotic and prebiotic supplementation have been cited for the elderly undergoing polypharmacy, those in hospitals or living in long-term care institutions or with an unbalanced intestinal ecosystem due to antibiotic therapy (Woodmansey, 2007). Intervention studies in the elderly are not very abundant, but the majority of them suggests that the direct manipulation of gut microbiota could improve health conditions (Pérez-Martinez et al., 2014). Scientific literature reviews have detailed the therapeutic effects of probiotics, prebiotics and their combination (synbiotics) (Toward et al., 2012; Biagi et al., 2013; Lakshminarayanan et al., 2014). However, until now, the administration

of these supplements (quantity, species or formulation) aimed at recovery of the microbiota does not seem to have taken into account the differences in this environment, secondary to the aging process or lifestyle. Few studies have mentioned the differences in administration of these supplements in relation to the previous aspects. It seems that we are far from being able to choose the exact combination of bacterial types or components that would properly correspond to each of the clinical environments in question (Lutgendorff et al., 2008).

Stsepetova et al. (2011) stress that the use of probiotics, prebiotics or symbiotics in the elderly must consider the structural differences in the bacterial communities found in them (Stsepetova et al., 2011). They identify that the number and distribution of the intestinal *Lactobacillus* species found in healthy adults and in the elderly have shown substantial structural differences and, therefore, any further intervention of these species should consider it.

The gut microbiota profile of the elderly might not be ideal, but there is also a recognition that the impact of diet needs to be better understood in order to identify dietary factors that provide substrates for the microbes. Armed with this knowledge, it may then be possible to intervene (with supplements) to establish desired changes in microbial populations, the products generated by them and the resulting health outcomes. It is necessary to understand exactly what constitutes a healthy microbial population in the intestines of the elderly (Conlon and Bird, 2015).

Arumugam et al. (2011) identified, through the genetic analysis of samples coming from six nationalities, three large group types that make up the human microbiota; *Bacteroides*, *Prevotella* and *Ruminococcus*. According to the authors, the composition of microbiota and presence of specific bacterial species is not dependent on age, gender or ethnicity. Wu et al. (2011), however, showed that microbiota is dependent on diet, with the enterotypes strongly associated with long-

term diets. The consumption of large quantities of saturated fat and protein determines the development of the *Bacteroides* enterotype, while *Prevotella* is present in individuals with diets rich in carbohydrates and fiber, and low in animal fat and protein. The enterotypes present in the intestine determines the metabolic products created, which can be beneficial or harmful, and the consequences for the host. The microbiota composition can change within a 24-hour period after modification of a high-fat/low-fiber or low-fat/high-fiber diet, but the type of enterotypes will remain unchanged for a longer time. Therefore, a diet can alter the microbiota composition in the short term, but enterotypes will only be modified with long-term diets (Wu et al., 2011). Changes in the overall composition of gut microbiota, nonetheless, in general only persist during the period of intervention (Conlon and Bird, 2015). Considering these aspects, the required time to cause modifications in the microbial population should be taken into account when considering a therapeutic intervention with probiotics or prebiotics (Saad, 2006; Martinez et al., 2015).

Notwithstanding this type of finding, the influence of macronutrients in the microbiota needs to be better elucidated, as carbohydrates have many effects that are not fully understood, and the impact of dietary fat and proteins is even less defined (Conlon and Bird, 2015). With increasing life expectancy, never has it been more important to build knowledge about the complex relationship between food choices, physical activity and microbiota diversity (Clarke et al., 2014).

Thus, beyond the aging process and diet itself, other factors that are currently ignored could also impact on the microbiota (Conlon and Bird, 2015) and must be considered when probiotics and prebiotics are being used.

Among the main factors related to lifestyle, the practice of physical exercise has also been associated with increased intestinal biodiversity (Clarke et al., 2014). Research evaluating the effects of exercise and diet on microbiota has demonstrated that athletes present a greater diversity of microbiota in comparison to controls of the same age, body mass index and gender. The greatest diversity correlated with protein intake, exercise and diet in the athlete group (Clarke et al., 2014). The types of food consumed by the athletes were different from the control group. The most significant differences were in relation to the consumption of fruits and vegetables by athletes and snacks by the controls (Clarke et al., 2014). Fruits and vegetables are sources of prebiotics, which could contribute, in addition to exercise, to the increased microbiota diversity found in athletes.

Results of studies evaluating physical exercise, diet and probiotics may help, in the future, to determine the most recommended probiotics for athletes and non-athletes, according to particular circumstances or type of sport. They can indicate which types and characteristics of exercise (intensity and duration) for men and women will have more influence on the microbiota, and which species, variety or combination of probiotics could be more beneficial (Counsell, 2015).

A sedentary lifestyle, in turn, is associated with health problems, very often with obesity and related disorders (O'sullivan et al., 2015). Exercise as a preventive strategy involves systemic adaptations of many different organs. It also promotes biological adaptations that influence the gut-brain-microbiota axis, diet-microbiota-host metabolic interactions, and neuroendocrine and neuroimmune interactions (O'sullivan et al., 2015).

Smoking is also among the factors related to lifestyle, since smoking significantly influences the composition of microbiota (Benjamin et al., 2012) and induces alterations in the microbial

population, which can contribute to an increased risk of cardiovascular disease. The toxic particles produced by the use of tobacco, similar to those transmitted in the air through environmental pollution, can reach the intestine, damaging the microbiota and, thus, influencing the development of intestinal diseases (Beamish et al., 2011). In individuals who stop smoking, a substantial alteration and increase in gut microbial diversity is observed. Furthermore, the pathogenic association between weight gain and smoking cessation is attributed to changes in the microbiota (O'toole and Korzenik, 2014). Perhaps the modulation of microbial diversity using probiotics and prebiotics can bring benefits to former smokers, even contributing to regulation of body weight.

Another important element present in modern life that has a major impact on the physiology of the intestine is stress. This can alter the profile of microbiota and impact on the motor activity of the colon through the gut-brain axis. A literature review was conducted by Lutgendorff et al. (2008) to evaluate the interaction between the commensal microbiota of the intestine and the intestinal mucosa during stress, and to assess the possibilities of using probiotics in neutralizing the deleterious effects. It was observed that probiotics may counteract changes in the intestinal barrier function, visceral sensitivity and the gut motility induced by stress (Lutgendorff et al., 2008).

Studies have been reported that also confirm the influence of microbiota on the mood and behavior of individuals (Grenham et al., 2011), with the elderly being more susceptible (Felice et al., 2015). Intestinal physiology, which is strongly influenced by the microbiota, plays an important role in the appropriate signaling that occurs along the gut-brain axis. Intestinal dysbiosis can negatively influence this signaling, with consequences for the central nervous

system functions (Grenham et al., 2011). Results of a randomized, controlled study testing the effect of a mixture of probiotics (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus brevis*, *L. casei*, *Lactobacillus salivarius*, *Lactococcus lactis*) in individuals without psychiatric or neurological disorders provided, according to the authors, the first evidence suggesting that the intake of probiotics can help reduce rumination and aggressive thoughts associated with a sad mood (Steenbergen et al., 2015).

Accordingly, the use of pro-, pre- and symbiotics in maintaining intestinal health in order to positively influence mental state has been considered a preventive strategy that is worth being implemented (Bischoff, 2011). The bidirectional signaling of the gut-brain axis is regulated by hormonal, immunological and neural pathways (Grenham et al., 2011), and among the neurological disorders, autism has also been associated with changes in the gut microbiota (Stilling et al., 2014; Jolanta Wasilewska and Klukowski, 2015). Aside from the fact that microbiota influences the development of neurological disorders, patients with neurological diseases very frequently present difficulties related to eating (food selection and limited variety), which contributes to dysbiosis. Therefore, therapeutic approaches using probiotics can be among the options for improving the bidirectional signaling of the gut-brain axis and, consequently, modifying cognitive and behavioral functions (Mulle et al., 2013; Douglas-Escobar et al., 2013). In relation to psychological outcomes, however, investigations in humans are still very restricted. A systematic review identified ten randomized, controlled, double-blind clinical trials assessing the effect of probiotic intervention in humans on their psychological outcomes or psychiatric symptoms, and all presented limited proof of the effect of this type of intervention on psychological outcomes (Romijn and Rudcklidge, 2015).

In addition to the cited factors, other aspects linked to the environment can influence the health of an individual by causing modifications in the microbiota, among them, poor sanitary conditions, more common in developing countries, inadequate personal hygiene, and travel (Verdu and Riddle, 2012). These situations contribute to the occurrence of acute infectious processes, sometimes undiagnosed, and may lead to chronic consequences, triggering long-term changes in intestinal physiology, especially in susceptible individuals like the elderly (Verdu and Riddle, 2012). In these cases, the use of probiotics has shown to be an alternative (Jeong et al., 2015).

Finally, a new environmental factor has been considered as a potential modifier of gut microbiota, namely, disruption of the circadian cycle. This disorganization can be provoked by numerous factors, such as prolonged travel, shift work (Voigt et al., 2014), and “social jetlag” (social calendar) (Wittmann et al., 2006), among others. One of the hypotheses regarding this influence is the disruption of the circadian cycle of the individual that, in turn, affects the microbiota circadian clock, altering its structure. There is as yet no proof the gut microbiota has an intrinsic circadian organization, independent from that of the host (Voigt et al., 2014). It is possible to conclude though that to live in opposition to our internal clock can contribute to metabolic dysfunction and its consequences (Parsons et al., 2015).

In real life, sleep opportunities, as well as its duration, quality and efficiency are strongly influenced by social schedules, meaning the difference between the endogenous and social clocks can produce interruptions in the circadian rhythm (Foster et al., 2013). Close to the age of retirement or with aging, a decrease in the impact of the social clock on sleep duration is observed (Foster et al., 2013). However, the aging process, besides very often being

accompanied by a decrease in professional and social commitments, also produces important alterations in sleep quality. Together these aspects contribute to a decline in temporal organization in the elderly. This disassociation between environmental signals and the sleep-wake cycle leads to several health problems (Copinschi et al., 1999), among them alterations in microbiota (Voigt et al., 2014).

Circadian clocks are regulated by light and food cycles, and, therefore, their adequate supply, as well as physical exercise, has a beneficial impact on the health of the individual, probably as they help maintain the synchrony of these cycles (Tevy et al., 2013). By way of analogy, one might think of using supplements like probiotics to maintain circadian cycles, which would improve the quality of sleep in the elderly due to its positive effects on the microbiota.

Several researches conducted with probiotics (in *in vitro* and clinical trials), together with recent studies using symbiotics in elderly health, have placed these elements as an interesting therapeutic intervention to minimize changes in the microbiota of elderly individuals. However, better identification is still needed of the ideal combination of probiotic organisms according to the specific niche that it is intended to address (Woodmansey, 2007).

FINAL CONSIDERATIONS

One of the biggest challenges of our time is to maintain balanced and healthy ecosystems, given the actions of mankind on nature, which have been intense, systemic and catastrophic over the past 200 years. These actions have a negative impact on human health and on its organic ecosystem. Gut microbiota is a diverse, complex and “intelligent” ecosystem that specializes in harmonious cohabitation of human niches.

These microorganisms have co-evolved with humans and promote benefits to their hosts, such as protection against toxic chemicals and pathogens, and improving and making the extraction of energy from food more efficient. However, the profound changes in human lifestyle and diet brought about by the Industrial and Agricultural Revolution have also created environmental selection pressures favoring pathogens specialized in colonizing human hosts, which is likely to cause an imbalance in the homeostasis (dysbiosis) of gut microbiota, promoting the onset of disease.

In this context, diet occupies a central role. The intake of “unnatural” foods (perhaps the most consumed in the world), i.e., those that have been contaminated, genetically modified, stored, transported, and processed with additives and preservatives, provides a smaller amount of complex polysaccharides (dietary fiber), while also giving greater amounts of chemicals harmful to health, which can damage gut microbiota. Intake of these foods can negatively alter this highly sensitive and specialized ecosystem. Typical western diets have a deleterious effect on the human microbiota as they contain high levels of cholesterol, small quantities of soluble and insoluble fiber, excess sugar and salt, and dietary restrictions (Maslowski and Mackay, 2011).

This detrimental effect results in reduced and undiversified gut microbiota with deficient and dysbiotic functioning. Furthermore, increased plasma endotoxin levels are frequently observed in the dysfunctional gut microbiota of the host. Endotoxins are integral components of the outer membrane of gram-negative bacteria, such as *Enterobacteriaceae* and *Pseudomonadaceae*, composed of proteins, lipids and lipopolysaccharides. The lipopolysaccharides are responsible for most of the biological properties of bacterial endotoxins,

and are known to have an exceptional ability to induce inflammation through the Toll-like receptors 2 (TLR2) and 4 (TLR4) (Bengmark, 2013).

Accordingly, some studies have demonstrated the essential role of microbiota in mediating the association between endotoxin plasma levels and chronic disease, especially metabolic disorders, Alzheimer's disease and cognitive decline (Mathew et al., 2003; Fassbender et al., 2004; Jaeger et al., 2009).

Evidence hitherto shows that host-microbiota interaction occurs right from cell-cell communication through to broad systemic signaling involving several organs. It also suggests that microbiota can be seen as an epigenetic entity, a mediator of gene-environment interaction (Beamish et al., 2011). In addition, it is important to consider this symbiotic harmonious relationship between the microbiota and human host. Ultimately, we humans are metabolically driven by our genome or by the effects of interaction with the microbial genome, since the microbiota metagenome is approximately 150 times larger than our own genome. If our health is dependent on this relationship it becomes essential that we adopt healthy lifestyle habits.

Both the aging process, environmental factors and lifestyle are associated with modifications in the microbiota. Consequently, the current challenge is to understand the extent to which these factors that interfere with the microbial profile in the intestine are interconnected, and how probiotic, prebiotic or symbiotic therapies should be conducted within this scenario. Therefore, these treatments should also be tested and regulated, with well-defined recommendations for their use, both in a healthy population and in the treatment of disease.

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