





SYSTEMIC ERYTHEMATOUS LUPUS AND GUT MICROBIOTA: A REVIEW ON ITS RELATIONSHIP WITH THE DEVELOPMENT OF CARDIOVASCULAR DISEASES FROM THE POINT OF VIEW OF CLINICAL NUTRITION

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune disease featuring pleomorphic clinical manifestations whose etiology basically depends on the abnormalities in the functioning of the immunological system coupled to environmental and hormonal factors characterized by the production of antibodies and immunocomplex deposition. People suffering from SLE are prone to have cardiovascular diseases when compared to people in general. Further, several studies suggest that intestine microbiota may have an important role in the progress of such diseases. Microbiota is generally associated with the functioning of the immunological system whose response gets worse due to intestine dysbiosis which may result in a chronic inflammatory stage and, consequently, great cardiovascular risk. Several authors discuss the mechanism by which response to microbiota takes place and the possibility of dietetic interventions. These may comprise probiotics to modify intestine dysbiosis to thwart the disease's progress and frequent cardiovascular disorders in the population. Current paper revises the available literature on the relationship between intestine microbiota and its nutritional characteristics in SLE patients and the development of cardiovascular diseases.

Keywords: *Systemic Lupus Erythematosus; Microbiota; Cardiovascular diseases*

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease featuring clinical pleomorphic manifestations whose etiology basically depends on abnormalities in the functioning of the immunological system coupled to environmental and hormonal factors characterized by the production of antibodies and immunocomplex deposition. The most common features comprise photo-sensitive skin lesions, constitution symptoms, changes in the hematological and lymphatic system, lupus nephritis, inflammation of joints and membranes. It may also attack the heart, lung and nervous system¹.

The disease, currently diagnosed by clinical criteria and laboratory tests, is more prevalent among young females and may have different manifestations with regard to chronicity, graveness and association with primary immunodeficiency, especially among young people and adults. In the case of people with earlier symptoms of the disease, particularly during childhood, a more serious phenotype may be extant²⁻⁵.

In its earlier stages, the disease's mortality condition is rather more linked to infection, followed by kidney or central nerval system issues, whilst in more advanced stages of the disease, there is an increase in cardiovascular causes associated with atherosclerosis, partially related to corticosteroid therapy and chronic inflammation⁶⁻⁸.

Studies on data derived from the Information System on Mortality of the Brazilian NHS Database (Datusus) with regard to SLE patients

have shown that a greater control of risk factors should exist in Brazil for cardiovascular diseases. Further, deaths related to infectious causes are the most frequent in the country and a better management is required especially with regard to the disease's early stages⁹.

Cardiovascular disease (CVD) is an important cause of early death¹⁰ and SLE patients have a greater number of risk factors, such as obesity, dyslipidemia and metabolic syndrome, when compared to the population in general⁸. Further, hypertension may be an important risk factor for cardiovascular episodes in this population¹¹.

The role of gut microbiota as an immunological response is still under analysis¹². Several studies have suggested that probiotics may be an aid in the decrease of the patients' intestine dysbiosis and may possibly thwart the advancement of the disease and cardiovascular disorders^{13,14}.

Current paper features a review of the available literature on the relationship of gut microbiota of SLE patients and the development of CVD from the point of view of clinical nutrition.

GUT MICROBIOTA

Human intestine microbiota hosts several micro-organisms that colonize the surface of the gastrointestinal tract¹⁵. Are mainly composed of strict anaerobes, and some facultative anaerobes. The composition of microbiota in healthy people is relatively stable, with six predominant bacterial phyla: Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria and Verrucomicrobia. There is a predominance of gram-positive Firmicutes, followed by gram-negative Bacteroidetes^{16,17}.

The Bacteroidetes and Firmicutes are conserved in almost all individuals, although the proportions of these phyla may vary. However, when considered at the level of bacterial species, the variation in the composition of interindividual microbial communities is considerably greater than that observed at the phylum level. It should be highlighted that the composition of gut microbiota differs along the digestive tract¹⁵.

Moreover, different factors may cause or may be related to changes in the gut microbiota due to its malleability and fragility within environmental and diet alterations which may include the use of antibiotics, place, pathologies, lifestyle, existence of fibers, aging, type of delivery and others^{15,17-19}.

It is a well-known fact that microbiota works out basic functions for the human organism, including digestion of nutrients, protection against pathogens, interaction with the immune system and the production of metabolites²⁰⁻²². Some intestinal bacteria can produce antimicrobial compounds and compete for nutrients and sites of attachment in the gut, avoiding colonization by pathogenic microorganisms.

As cited before, the gut bacteria are also able to produce a variety of vitamins, synthesize amino acids and perform biotransformation of bile. In addition, the microbiome is related to biochemical pathways for the metabolism of nondigestible carbohydrates, which include large polysaccharides. As result of this, occurs a recovery of energy and substrates for the host and for bacterial growth and proliferation.

The microbiota may be considered a virtual and metabolic organ²³ which as a rule acts as a physical, functional and immunological barrier of the gastrointestinal tract²⁴. Consequently, it is of paramount importance to observe that changes in the microbiota's state of equilibrium, from eubiosis to dysbiosis, may result in the loss of health's good effects²⁵.

Further, it should be highlighted, together with the mucous barrier and the gut associated lymphoid tissue (GALT), microbiota form a defense intestine barrier, with GALT as a communication vehicle of lymphocytes T and B with cells from other tissues and production of immunoglobulin A²⁶. Consequently, they have a crucial role in the proper functioning of the immune system.

MICROBIOTA AND SLE

There is evidence of a possible interference of gut microbiota in SLE (Table 1). A study on animal models has shown decrease in gut microbiota diversity in diseased mice when compared to animals of the control group. Pathology is, therefore, associated to changes in gut microbiota. The authors showed that the microbiota of mice with lupus may induce the production of antibodies, stimulate inflammatory immune response and positively regulate genes' susceptibility to SLE in germ-free mice. They also suggest that microbiota have a relevant role in SLE pathogenesis, even though further assays are needed to determine the specific microbial species related to the process and to the mechanism involved²⁷.

Table 1: Findings about microbiota in patients and animal models of SLE.

First author, year	Type of study	Sample	Microbiota in SLE
Zhang et al., 2014	Experimental	Murine lupus model × age-matched healthy controls	↓ Lactobacilli ↑ Lachnospiraceae and overall diversity
Hevia et al., 2014	Cross-sectional	20 SLE patients in remission × 20 age- and sex-matched healthy control subjects	Diversity comparable based on Shannon's index ↓ Firmicutes/Bacteroidetes ↓ some Firmicutes families
Johnson et al., 2015	Experimental	Mouse model of SLE Female mice Acidic pH drinking water (AW) × Neutral pH drinking water (NW)	↓ β-diversity and ↑ Christensenellaceae family in AW recipients Firmicutes/bacteroidetes ratio was not significantly different ↑ Rikenellaceae Family in NW recipients
Zegarra-Ruis et al., 2019	Experimental	Toll-like receptor 7 (TLR7)-dependent mouse models of SLE	Culture of internal organs and 16S rDNA sequencing revealed TLR7-dependent translocation of <i>L. reuteri</i> in mice and fecal enrichment of <i>Lactobacillus</i> in a subset of SLE patients
Toral et al., 2019	Experimental	Female mouse model of lupus × control groups	↑ <i>Pedobacter</i> , <i>Lactobacillus</i> , <i>Prevotella</i> LC40 treatment ↑ <i>Bifidobacterium</i>
Ma et al., 2019	Experimental	TC (SLE) mice × Control mice (C57/B6) All mice were female	↓ Community richness ↓ Diversity

One of the first studies with SLE people revealed a decrease in the amount of Firmicutes and in Firmicutes/Bacteroidetes ratio²⁸, when compared to healthy controls. The ratio has been related to health conditions since it affects the production of short-chain fatty acids with acknowledged benefits. Firmicute-produced butyrate, one of the fatty acids acknowledged for its role in intestine health, interferes in the differentiation of regulatory T cells in the intestine, spleen and lymph system by suppressing inflammation, one of SLE characteristics. Consequently, decrease of Firmicutes and the reduction of butyrate may contribute towards the patients' inflammation conditions. Increase of Bacteroidetes has been related to an increase of Toll-like Receptor-4 (TLR-4), the latter being associated to the spontaneous development of SLE²⁹.

Another study provided data on the microbiota of SLE patients, showing a significant increase of the genera *Lactobacillus*, *Streptococcus*, *Megasphaera*, *Fusobacterium*, *Veillonella*, *Oribacterium*, *Odoribacter*, *Blautia* and *Campylobacter*, whereas a decrease of the genera *Faecalibacterium*, *Roseburia* and species *Ruminococcus gnavus* may be observed in receding disease, or rather, it denoted a difference in microbiota according to the disease's activity³⁰.

The composition of intestine microbiota in males and females may also be a relevant factor when one takes into account a greater diagnose ratio in females. Estrogen and its receptor are

also related to an increase in TLR-4 activity³¹. Research works that focus on the relationship between intestine microbiota and SLE, particularly the predominance of the disease in females, would be highly relevant³².

RELATIONSHIP BETWEEN MICROBIOTA AND CVD

Risks of development of CVD are high not merely among obese people but in people suffering from several self-immune diseases, among which SLE may be mentioned²⁹. Several studies suggest the importance of microbiota within the context of cardio-metabolite diseases, comprising cardiovascular diseases, obesity, diabetes, non-alcohol hepatic steatosis, atherosclerosis, hypertension and dyslipidemia^{24,33-39}, or rather, conditions in which a pro-inflammation condition and intestine dysbiosis are extant.

Although the mechanism related to the development of CVD in patients with self-immune diseases is still unknown, inflammation is highly relevant²⁹. In the case of SLE, chronic inflammation has been associated with atherosclerosis lesions. Further, thrombosis, arthritis, vascular spasms have also been reported, or rather, leading towards coronary arterial diseases or coronary cardiovascular diseases.

An increase in TLR-4 activity related to an increase of Bacteroidetes in the patients' microbiota may have an important role in the development of several

cardiovascular diseases since TLR-4 activation by lipopolysaccharides (LPS) may increase CD40 levels in macrophages and microglia in the hepatic and kidney tissues, linked to the activation of the immune response and taking into account that the increase of CD40 in macrophages are related to pathogenesis of atherosclerosis and atherothrombosis^{40,41}.

Several authors have thus shown that SLE-associated cardiovascular risk would be the result of an immune response increased by a great number of antigen-providing bacteria, such as Bacteroidetes and Lachnospiraceae, coupled to a decrease of Firmicutes and, consequently, butyrate, dysfunction of T cells (deregulation Treg/Th17), starting and continuing a chronic condition state^{29,30}.

DIETETIC INTERVENTIONS: RELATIONS WITH MICROBIOTA, SLE AND CVD

As mentioned above, intestine microbiota has a relevant role in the metabolic function, maintenance and homeostasis of the immune system, activity against pathogens and the maintenance of the epithelial barrier. It seems that differences exist in the intestine microbiota of slim and obese people and between people with different dietary habits. However, there is a relationship between diet, inflammation, resistance to insulin and cardiometabolic risk which may be linked to the composition of bacteria of the intestine microbiota⁴². Several studies discuss this relationship (Table 2).

Table 2: Studies and reviews that found and/or discuss relation between diet and microbiota that may be related to cardiovascular risk.

First author, year	Type of study	Dietetic factor	Microbiota and cardiovascular risk factors
Moraes et al., 2014	Review	High fat diet, prebiotics, probiotics	Dietary patterns interfere with the composition of the microbiota and have relevance in metabolic modulation and regulation of body adiposity. Higher proportion of Firmicutes in relation to Bacteroidetes it is related to obesity and metabolic disorders.
Marques et al., 2017	Experimental, animal model	High fiber diet and supplementation with the short-chain fatty acid (SCFA) acetate	A diet high in fiber led to changes in the gut microbiota which played a protective role in the development of cardiovascular disease. The favorable effects of fiber may be explained by the generation and distribution of one of the main metabolites of the gut microbiota, the SCFA acetate. Acetate effected several molecular changes associated with improved cardiovascular health and function.
Djekic et al., 2020	Randomized crossover study	Isocaloric vegetarian diet versus meat diet	Differences between vegetarian diet and meat diet were observed in the relative abundance of several microbe genera within the families Ruminococcaceae, Lachnospiraceae, and Akkermansiaceae. The vegetarian diet in conjunction with optimal medical therapy reduced levels of oxidized LDL-C, improved cardiometabolic risk factors, and altered the relative abundance of gut microbes and plasma metabolites in patients with ischemic heart disease. Results suggest that composition of the gut microbiota at baseline may be related to the reduction of oxidized LDL-C observed with the vegetarian diet.
Kono et al., 2021	Review	High fat diets	The long duration of high disease activity is a significant risk factor for cardiovascular events. A high-fat diet can give rise to dysbiosis, and patients who are affected by obesity and/or have SLE possess less diverse microbiota.
García-Monteiro et al., 2021	Review	Western Diet (WD) Versus Mediterranean Diet (MD)	Diet must be the most important environmental factor positively or negatively affecting both gut microbiota and immune system. WD is characterized by low-quality "food matrix" and is a pattern in countries where NCDs, obesity, T2DM, MetS, CVD, and IBD are prevalent. Adherence to an MD may ameliorate inflammation and gut microbiota dysbiosis, thanks to its abundance in PUFAs, dietary fiber, polyphenols, vitamins and trace elements.
Xu et al., 2021	Meta-analysis of randomized controlled trials	Microbiota-accessible carbohydrates (MAC)	When compared with lower intake, increased MAC intake improved glycemic control, blood lipid, body weight, and inflammatory markers for people with T2DM.

NCDs: Noncommunicable diseases; T2DM: Type 2 diabetes mellitus; MetS: Metabolic Syndrome; CVD: cardiovascular disease; IBD: intestinal bowel disease; PUFA: polyunsaturated fatty acids.

Evidenced and above-mentioned imbalance can also refer to the Bacteroidetes and Firmicutes ratio. In fact, Firmicutes are relevant for the absorption of fatty acids and energy of carbohydrates, whereas Bacteroidetes are also important in the absorption of polysaccharides⁴³. Changes in micro-organisms may be related to weight gain and obesity, a condition with chronic inflammation. This fact would highlight need of caution regarding weight in SLE cases.

Consequently, it is highly important to understand the role of different genera and species in diverse weight-related mechanisms since diversity of micro-organisms of intestine microbiota may affect body adiposity and not merely the number of phyla⁴⁴. In fact, the phylum Firmicutes has more than 250 genera, whereas Bacteroidetes has approximately 20⁴⁵. The above may be related to divergences in studies on obesity and SLE cases⁴², even though diet is a crucial factor in this context.

Caution should be taken on the relationship between obesity and its comorbidities, diets rich in fats and self-immune diseases, among which SLE may be mentioned. According to a hypothesis by Kono et al., obesity may affect immune response and contribute towards SLE pathogenesis. The above may be related to changes in adipokines (increase in leptin and adiponectin), deficiency in vitamin D and intestine dysbiosis caused by diets rich in fats⁴⁶. Excessive consumption of fats, particularly saturated and trans fats, would, in itself, be a risk factor for cardiovascular episodes⁴⁷. Since great activity of SLE during a long period is a risk factor for cardiovascular events, further studies that would investigate the impact of diet and alterations in microbiota within the context of SLE for the analysis of the relationship in the outcome, are crucial for their decrease. The literature on such an approach is rare, even though several studies are extant on the relationship of such aspects.

Several authors have compared the components of Western and Mediterranean diets with special reference to changes in microbiota and immune system. The nutritional condition and cardiovascular diseases, diseases related to inflammation coupled to deficient immunity and commonly with intestine dysbiosis are mentioned²². Diet is related to the modulation of the immune system and intestine microbiota simultaneously. It establishes a two-way communication with the signalization of paths and the production of metabolites that affect each other's function. The authors underscore that deficiencies of micronutrients usually present in malnutrition cases are determinant in the physiopathology of immunodeficiencies and inflammatory diseases such as obesity, metabolic syndrome, diabetes type 2, intestine inflammatory disease and others. They are common diseases especially in developing countries which follow a Western diet rich in carbohydrates and

saturated fats, refined food rich in sugars and additives, and ultra-processed foods. On the other hand, it should be underscored that the Mediterranean diet, rich in polyunsaturated fatty acids, fibers, polyphenols, vitamins and trace elements, such as zinc, iron and selenium, may decrease inflammation and dysbiosis. The diet is an aid in Th17/Treg equilibrium and maintains the diversity of intestine microbiota²². Nutrient-rich foods, such as those that comprise the Mediterranean diet, may decrease inflammation caused by diets poor in nutrients and rich in calories, lowering cardiovascular risk factors. Due to its metabolic assets, it is the diet recommended by the American Diabetes Association⁴⁸. However, we may underscore several food components in Mediterranean diet which may be relevant in SLE cases when cardiovascular risks are involved.

Microbiota-accessible carbohydrates (MAC), non-digestible oligosaccharides and polysaccharides in the soluble fibers of the diet (fruit-oligosaccharides, insulin, resistant starch, Beta glucan, pectin) are crucial for the maintenance of the intestine's microbial ecosystem, whereas poor diets are related to the loss of intestine diversity^{49,50}. Fiber-rich diets are associated with a decrease in arterial pressure, improvement of metabolism, changes in intestine microbiota with protection in the development of cardiovascular diseases^{22,49}. Marques et al. report that fibers' positive effects are due to the generation and distribution of the intestine microbiota's metabolites, such as short-chain fatty acid acetate. Studies in animal models revealed that high consumption of fibers increased the number of acetate-producing bacteria in the microbiota regardless of excess of mineral corticoids employed. Fibers and acetate supplements improved the Firmicutes/Bacteroidetes ratio, reduced systolic and diastolic arterial pressure, heart fibrosis and left ventricular hypertrophy when compared to control animal groups. The authors hypothesize that the acetate may be the cause of several molecular changes associated with an improvement of cardiovascular function and health⁵¹.

On the other hand, the consumption of extra virgin olive oil, rich in monounsaturated fatty acids would increase the bacteria *Bifidobacterium* and *Lactobacillus* and their bioactive metabolites in GALT. The process would reduce pro-inflammatory factors and arterial pressure and stimulate the production of butyrate by microbiota. Further, polyunsaturated fatty acids Omega 3 seem to be favorable to microbiota and interfere positively in the Firmicutes-Bacteroidetes equilibrium, increasing Lachnospiraceae and *Bifidobacterium* families and reducing the growth of LPS-producing enterobacteria, with anti-inflammatory results²².

Richness in polyphenols constitutes another characteristic of Mediterranean diet due to abundance of fruit, spices, herbs, olives and oleaginous products in the diet. Polyphenols, characteristics

of the diet, comprise hydroxytyrisol in extra virgin olive oil, resveratrol in grapes and quercetin in onions, broccolis, apples and others. In fact, hydroxytyrisol increases bifidobacteria with anti-inflammatory and antioxidant activities²².

It seems that the effects of meatless diets are highly positive towards microbiota and cardiometabolic risks according to a randomized study with patients suffering from ischemic cardiac disease which evaluated the effects of vegetarian diets and diets with meat. Vegetarian diet coupled to proper medicament therapy decreased the levels of oxidized LDL-C, improved the factors of cardio-metabolic risks and changed the number of intestine microbes and metabolites in the plasma of patients with ischemic cardiac disease. Differences between the vegetarian diet and meat diets were characterized by the abundance of different microbial genera within the Ruminococcaceae, Lachnospiraceae and Akkermansiaceae families. There is a lower rate of the first two families and a higher rate in the latter family in the vegetarian diet⁵².

In the wake of already mentioned mechanisms and innovatory ones, one may analyze the production of short-chain fatty acids, secondary biliary acids and the recent discovery of trimethylamin (TMA)/trimethylamin N-oxide (TMAO), participants in the development and progression of cardiovascular diseases⁵³. TMAO is produced from dietetic precursors with TMA, such as phosphatidylcholine, choline and L-carnitine. These nutrients, found in fat-rich food, especially in fish, produce TMA through multiple enzymatic microbial complexes of the small intestine, composed of Firmicutes, Proteobacteria and Actinobacteria⁴⁷. High TMAO rates in the blood have been associated with cardiovascular risk, prevalence of DCV, worsening of prognostic and increase in death risks, probably due to severity of the inflammatory response of the vascular wall and the production of TMAO-caused oxygen reaction species⁴⁷. Early studies have revealed a high association between intestine microbiota-dependent phospholipidic metabolism and atherosclerosis risks mediated by the generation of pro-atherosclerotic TMAO metabolite. Analyses have been undertaken on the possibility of intestine microbiota as a new therapeutic target in CVD⁵³.

Further, several authors have analyzed aspects of the diet and the relationship with self-immune diseases. They have hypothesized that the good effects of calorie restriction in self-immune models, including lupus, may be partially mediated by the effects of intestine microbiome and associated virome⁵⁴. They suggest that alterations in diet-related intestine microbiota are one of the reasons for well-known but inexplicable fluctuations of self-antibody levels in self-immune and asymptomatic patients.

Since diet modifications may change SLE progress, it may be said that the relationship is

partially mediated by the effects of the gut microbiota. A study on SLE animal models showed that even small diet changes, such as pH of water, may affect the composition of intestine microbiota and SLE occurrence. The same assay revealed that mice which took acid pH value developed nephritis at a slower rate than those which received water with normal pH value. Further, mice which took water with normal pH value had higher circulating antinuclear self-antibodies levels than those who received water acid pH value, among other results⁵⁵.

Although SLE is the focus of current paper, it would not be preposterous to analyze certain mechanisms by which microbiota participate in the physio-pathological processes highlighted in a review that evaluated the relationship between microbiota and cardiometabolic risks, such as the suppression of Fasting-Induced Adipose Factor (FIAF), inhibition of 5'-adenosin-monophosphate protein kinases path (AMP-Q), stimulus to free fatty acids receptors (FFAR) and LPS translocation. The above mechanisms are involved in the deposition of fatty acids, increase of body adiposity, stimulus to inflammatory cytokines and resistance to insulin, which jeopardize the cardio-metabolic profile⁴² and should be further investigated within the SLE context.

In fact, several studies had similar or complementary results, reinforcing the need for further studies properly designed by diet factors to evaluate microbiota-mediated alterations with special focus on SLE to investigate possible causal relationships with CVD. Several types of food and micronutrients which have not been mentioned in this review should be analyzed due to their potential in the modification of microbiota and immune system. They may impact CVD which is a very fertile field for investigation and with different intervention possibilities.

THE USE OF PROBIOTICS IN SLE WITHIN THE CVD CONTEXT

Since the relationship with microbiota is not completely known, in the case of probiotics in the context of SLE and specifically with regard to DCV, most studies have been undertaken with animal models, with interesting results. Toral et al. investigated whether the bacterium *Lactobacillus fermentum* CECT5716 (LC40) would improve the disease' activity and cardiovascular complications in a female model with lupus. Treatment with LC40 decreased lupus activity, arterial pressure, heart and kidney hypertrophy and splenomegaly. LC40 decreased T and B cells in the mesenteric lymph nodes and the plasma concentration of pro-inflammatory cytokines. The endothelial dysfunction related to the production increase of superoxide conducted by NADPH oxidase and phosphorylation of eNOS became normal after

a 15-week treatment with LC40. Plasmatic levels of LPS also decreased and may be related to an improvement in the integrity of intestine barrier. Treatment also increased the amount of Bifidobacterium in the gut microbiota of mice with SLE. The authors concluded that manipulation of intestine microbiota with LC40 may be an alternative for the prevention of SLE-associated vascular damage¹³.

Another study revealed that the ingestion of retinoic acid may provide a decrease in SLE symptoms and normalize lactobacilli levels in lupus-prone mice. The study also showed that intestine colonization by Lactobacillaceae was negatively co-related with lupus activity. Consequently, the authors suggested that probiotics with lactobacilli may decrease the gravity of inflammatory crises of people suffering from lupus. Results were increased by an association with retinoic acid⁵⁶. Increase of lactobacilli in mice models may reduce inflammation by an increase in the production of IL-10 and regulator T cells⁵⁶⁻⁵⁸. However, in another study with animal models, *L. reuteri* (strain SP-C2-NAJ0070) featured to be an exacerbator of SLE symptoms in a different way other than TLR7, an effect which is not attributed to other lactobacilli⁵⁹.

When the specificities and different approaches of the above-mentioned studies are taken into account, one should highlight that the means by which commensal organisms show pathogenic or beneficial trends depend on factors such as diet, host's genetics, ingestion of drugs and others. Approaches with sequences of metagenomic ribosome DNA or 16S, the exclusive genome accessory of each strain and not merely phylogeny, may be relevant²¹. Consequently, such context should be taken into account with regard to the planning of approaches with probiotics for diseases such as SLE to ward off CVD.

Result of studies with probiotics in SLE patients for the prevention of kidney and cardiovascular diseases should be received with caution due to behavior difference of animal and human gut microbiota. Since the abundance of lactobacilli seems to be normal in patients with receding SLE, further analysis on the composition of microbiota should be undertaken for

the planning of interventions with the proper probiotic and which effectively impacts on the outcome of the disease. In fact, quantity and quality of the proper micro-organisms should be observed to obtain the good effect of probiotics. Several authors warn that fermented food with probiotics may not be an interesting option since it has only few amounts of probiotic organisms. Further, there is only scanty evidence on the role of probiotics as modulators of microbiota in the human intestine and very little is known on the microbiota of SLE hypertensive patients which is an important factor in the development of cardiovascular diseases. They suggest that bacteria, such as *L. fermentum*, which seem to reduce dysbiosis, improve the function of the intestine barrier and reduce endotoxemia, may be able to prevent vascular complications in patients with SLE. However, further studies should be undertaken for the use in clinical practice¹⁴.

CONCLUSION

In spite of evidences in the literature relating SLE and the interaction with bacteria in gut microbiota, further studies are required to analyze the relationship and the manner it affects the development of cardiovascular diseases in patients. Exploratory investigations which evaluate and follow up the patients, the development of co-morbidities, the use of drugs, especially antibiotics, and short- and long-term alteration of the microbiota, may be promising so that diet interventions, included probiotics, may be planned in a more precise and adequate way according to the impact of outcome.

Conflicts of interest

The authors declare no conflicts of interest.

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