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DOI 10.1055/a-0885-7169
Horm Metab Res 2019; 51: 326–329

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Postbox 30 11 20
70451 Stuttgart, Germany
ISSN 0018-5043

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Lipid Profiles in Lyme Borreliosis: A Potential Role for Apheresis?

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Key words
lipidapheresis, borreliosis, inflammation

received 01.02.2019
accepted 26.03.2019

Bibliography
DOI https://doi.org/10.1055/a-0885-7169
Horm Metab Res 2019; 51: 326–329

ISSN 0018-5043

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ABSTRACT

Dyslipidemia and dyslipoproteinemia are common causes of metabolic and cardiovascular diseases. On the other hand, intracellular bacteria, such as Borrelia burgdorferi, utilize host lipids to survive and disseminate within the host. Recent data suggest that elevated lipids are a contributing factor to the maintenance and severity of Lyme disease and its complications. Here we review and discuss the role of lipids in Borreliosis and report on a pilot trial to examine the potential roles of circulating lipids and lipoproteins in patients with Borrelia infection. In this analysis we assessed the clinical and lipid profiles of 519 patients (319 women, 200 men) with a proven history of Lyme disease, before and after an extracorporeal double membrane filtration. Lipid profiles pre- and post-apheresis were analyzed in conjunction with clinical symptoms and parameters of inflammation. Circulating cholesterol, triglycerides, LDL, LP(a), and other inflammatory lipids were significantly reduced after the apheresis, while symptoms of the disorder and bioindexes of inflammation such as CRP improved. Further studies should be initiated to investigate the possibly causal relation between Lyme disease and circulating lipids and to design appropriate therapeutic strategies.

Introduction

Borrelia bacteria recruit and metabolize host lipids that are essential for their growth and survival [1]. Therefore, Lyme disease caused by Borrelia burgdorferi requires cholesterol for survival of the microbe in vivo. Cholesterol acquired from the environment is a prerequisite for the formation of cholesterol glycolipids that need to be incorporated into the membranes of Borrelia. Furthermore, cholesterol and cholesterol-glycolipids, that are crucial for bacterial fitness, are antigenic and play a role in mediating interactions with cells of eukaryotic organisms infected with Borrelia burgdor-

feri [2]. Recent data demonstrated that dyslipidemia could be a risk factor for enhanced severity in Lyme disease [3]. Thus, in apolipoprotein E (apoE) – deficient and low density lipoprotein receptor (LDLR) – deficient mice that exhibit a prominent hypercholesterolemia, infection with B. burgdorferi led to an increased number of spirochetes in the joints and inflamed ankles of the animals with elevated cholesterol levels [3].

Hyperlipidemia is extremely common in our modern Western society, suggesting that elevated cholesterol levels might constitute a risk factor for more widespread, prolonged, and severe forms of Lyme disease. On the other hand, various infectious agents, including spirochetes, are associated with atherosclerosis and cardiovascular complications [4]. In regions with endemic Lyme disease, seropositivity for anti-Borrelia IgG antibodies was independently associated with atherosclerosis [4]. Hence, exposure to spirochetes may increase the risk for atherosclerosis. Borrelia burgdorferi was even implicated in carotid plaque disease [5].

In this study, we analyzed the clinical and lipid profiles of patients with a proven history of Lyme disease before and after an extracorporeal double membrane filtration. Lipid profiles pre- and post-apheresis were analyzed in conjunction with clinical symptoms and indexes of inflammation.

Materials and Methods

A total of 519 patients (319 women, 200 men) with an established diagnosis of Lyme disease were enrolled in this study. In all patients, the initial diagnosis of Lyme disease had been established by clinical signs, including the appearance of a cutaneous lesion as an erythematous annular rash with a centrifugal extension following a tick bite. In line with current guidelines for the diagnosis of Lyme disease in routine clinical practice, all patients underwent a two-tier serological testing using an ELISA as a screening test, followed by an immunoblot [6].

The average age of women was 51.7 years and that of men 49.3 years. Body height women: 165.6 cm and men 178.8 cm; Body weight women 64.7 kg and men 79.1 kg. The body mass index calculated from these measurements was 23.6 kg/m² in women and 24.7 kg/m² in men.

In all patients, an extracorporeal double membrane filtration (INUSpheresis®) was performed. The mean plasma turnover in women was 2.276 ml and in men 3.276 ml. The mean treatment time was 115 min. Patient informed consent was received from all patients for this pilot study.

In all patients circulating triglycerides, cholesterol, LDL, HDL, Lp(a), Lp-PLA2, and CRP were determined (Saarstedt Serum, Labor IMD, Dr. Baehr Berlin, Labor Synlab Weiden). Statistics was performed by KB Medical Consulting GmbH, Cham employing a two-tailed *t*-test.

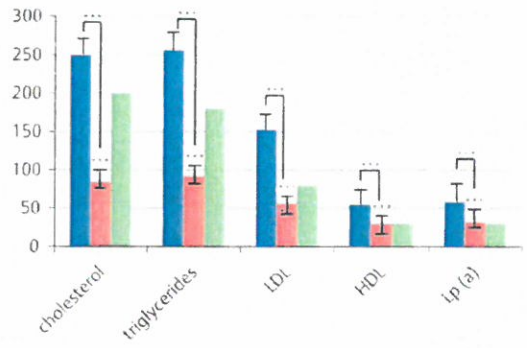
Results

Patients in this pilot trial had an established diagnosis of Lyme disease and a high level of suffering, with a Burrascano score above 3 (normal < 1). They presented with a significant elevation of LDL, lipoprotein (a) and inflammatory lipids, such as lipoprotein-associated phospholipase A2 (Lp-PLA2), as compared to normal reference values. They also had a significant increase in CRP, as compared to unaffected reference values. In contrast, oxidized LDL (MDA-LDL) levels were not significantly higher in the patient group than reference values.

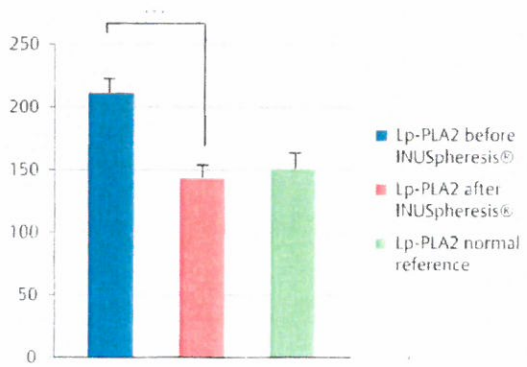
Following extracorporal double membrane filtration (INUSpheresis), there was a clinical improvement with a 70 % decrease in cholesterol, triglycerides and LDL levels while Lipoprotein (a) levels were reduced by 50 % (▸ **Fig. 1**). Lp-PLA2 levels declined by 40 % (▸ **Fig. 2**). There was a 3-fold decrease in CRP levels following apheresis (▸ **Fig. 3**).

Discussion

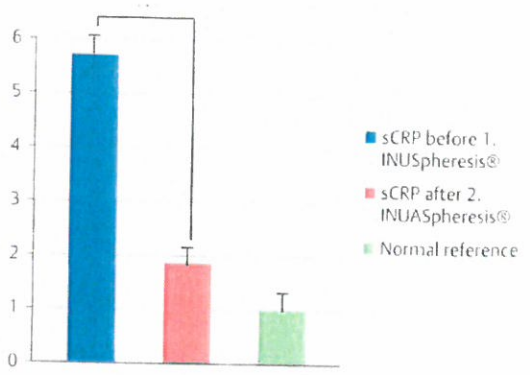
Patients who had experienced an exposure to Borrelia and exhibited clinical signs of Lyme disease with a significant level of suffering had elevated circulating lipid levels compared to an age-matched normal reference population. It was previously shown that patients with Lyme arthritis or neuroborreliosis demonstrated distinct plas-



▸ **Fig. 1** Lipid profile in patients with Lyme disease before and after extracorporal double membrane filtration (INUSpheresis®) (n = 519, ***p < 0.001).



▸ **Fig. 2** Lipoprotein associated phospholipase A2 (LP-PLA2) levels in patients with Lyme disease before and after apheresis (***p<0.001).



▶ **Fig. 3** CRP levels in patients with Lyme disease before and after apheresis (* * * $p < 0.001$).

ma lipidomic profile signatures. This was based on a comprehensive analysis employing LC-MS/MS, and these altered lipid profiles were suggested as potentially useful biomarkers for the diagnosis of invasion of the central nervous system and/or the joints [7, 8].

The causes of elevated lipids, including LDL, triglycerides, and other inflammatory lipids in patients with Lyme disease may be several and complex. Thus, they may range from a common genetic predisposition to dyslipidemia as is known in Western societies, to metabolic, inflammatory and psychosocial stress associated with the infection and the long-term complications of the disease. Patients do have inflammatory stress inferred by a significant increase in inflammatory biomarkers, including CRP and various cytokines. Furthermore, patients suffer from a persistence of clinical complications, as documented by decreased quality of life scores and increases in circulating cortisol.

The most rapid and efficient way to remove lipids from the human body is through plasma apheresis. Apheresis has been widely used in patients with familial hypercholesterolemia or other lipid disorders involving therapy-refractory elevations of triglycerides, cholesterol or lipoprotein (a) [9–12]. Lipid apheresis has been the most reliable method available to prevent and reduce cardiovascular events in patients with severe lipid disorders [9–12].

Elevation of LDL and triglycerides in patients with Lyme disease may suggest the need for treatment and effective elimination of lipids and inflammatory proteins. This is based on recent experimental data demonstrating that hypercholesterolemia results in more severe and prolonged infections with Borrelia [3]. Reduction of cholesterol and triglycerides could, however, be achieved also by a simple medical treatment with statins or other lipid-lowering drugs. Unfortunately, this therapy would not be expected to influence other inflammatory lipids and proteins that have been implicated in the pathogenesis of Lyme disease and the maintenance of chronic disease.

Oxidized phospholipids have recently been identified as an unifying link explaining the causal relations of lipoprotein (a) and cardiovascular disease [13]. Indeed, significant increases in circulating lysophosphatidylcholines and sphingomyelins were observed in patients with Lyme disease and correlated with central nervous system invasion (neuroborreliosis) [7]. In our study, we demonstrated a significant decrease in lysophosphatidylcholines.

Eicosanoids and related bioactive lipid mediators derived from polyunsaturated fatty acids seem to orchestrate an "inflammatory storm" through the wide-spread activation of inflammatory receptors by infectious agents, including spirochetes [14]. This may trigger an "inflammatory memory" driving the disease process into a chronic state, even in the absence of an infectious burden. Finally, Borrelia burgdorferi infection itself induces lipid mediator production during Lyme arthritis [15]. This includes eicosanoid biosynthetic pathways mediating inflammatory responses, triggering possibly not only acute arthritis, but other long-term autoimmune reactions [15].

The great advantage of the double membrane apheresis used in our setting is the removal of all these classes of lipids, including phospholipids, ceramides, sphingomyelins and eicosanoids [16]. Such a comprehensive reduction of all lipid classes that have been implicated in the aggravation and maintenance of chronic Lyme disease may constitute a powerful therapeutic tool for these patients. The results presented in this study, including a large number of patients that had a significant improvement of their symptoms and other frequent complaints, may indeed corroborate a causal link. An improvement of symptoms would be expected on the basis of the apheresis of bacterial toxins and/or the circulating inflammatory mediators and this is testable.

Patients were evaluated by different clinical scores, such as the Burrascano Score before and after treatment that suggested clinical improvement. These scores have a strong subjective component and therefore we focused on the clinical lab parameters.

However, given the complexity of the disease process and the subjective nature of the available disease scores, a firm cause-and-effect relation cannot be proclaimed. Apheresis treatment may even induce a significant placebo effect. Thus, to rule out nonspecific effects, further mechanistic studies, and randomized controlled trials, including a sham-treated patient group, would be required.

Given the evidence that [1] lipids are implicated in the pathogenesis and severity of Lyme disease and its complications [2], and the fact that elevated LDL and triglycerides are a significant risk factor (particularly in combination with inflammation) for cardiovascular disease, and [3] the documented risk of patients with Lyme disease for other atherosclerosis, ischemic strokes and carditis [17, 18] and, [4] finally, the role of cardiometabolic disturbances, including obesity and dyslipidemia, may suppress innate immunity and allow neuroborreliosis [19, 20]. These data clearly justify the need for further studies providing individualized and effective treatment for this patient group.

Acknowledgements

This work was supported by Transcampus.

Conflict of Interest

Richard Straube, Karin Voit-Bak, A. Gor, Til Steinmeier are working in the INUS Clinic. Stefan Bornstein is an advisor for INUS. All other authors have no relation to INUS.

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