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Plasma lipidomic profile signature of rheumatoid arthritis versus Lyme arthritis patients

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ABSTRACT

Objectives: Distinguishing of rheumatoid arthritis (RA) and Lyme arthritis (LA) is difficult, because of similar symptoms. This presents a significant clinical problem since treatments are quite different in both diseases. We investigated the plasma phospholipid profiles of RA and LA patients versus healthy subjects to find metabolic changes responsible for differentiation of both diseases.

Methods: Plasma was collected from 9 RA, 9 LA, and 9 healthy subjects. Extracted lipids were analyzed using LC-MS/MS to characterize phospholipid profiles of RA, LA and healthy subjects. Principal components analysis (PCA), partial least squares-discriminate analysis (PLS-DA) and variable importance in projection (VIP) scores were used to estimate the importance of each phospholipid variable.

Results: We identified 114 phospholipids in plasma. Phospholipid profiles were significantly different in RA and LA patients than in healthy subjects. Principal discriminant phospholipids between RA and LA groups were LPE (14:0), LPC(14:0) PI(18:0/20:4), PI(18:2/18:0), PI(16:1/18:2), PI(18:1/18:0), and PI(18:0/20:3).

Conclusions: Our study provides insights into the alteration of the plasma phospholipid profile of LA patients, resulting from *Borrelia burgdorferi* infection, that may lead to improved LA diagnosis and differentiation of this disease from RA. Furthermore, LPE (14:0) was found to have a high potential to be a possible biomarker of LA.

1. Introduction

Musculoskeletal disorders comprise over one hundred different diseases, including rheumatoid arthritis (RA) and Lyme arthritis (LA), which present similar symptoms, such as joint pain and inflammation. RA is an autoimmune disease caused by genetic and environmental factors, while LA is known as a late manifestation of Lyme disease caused by the spirochete *Borrelia burgdorferi* transmitted to humans by tick bites [1]. In LA, large joints, e.g. the knee, shoulder, or elbow, are especially affected, while in RA, small joints are also affected [1,2]. Both untreated RA and LA lead to joint deformity and disability. Unfortunately, joint manifestations during the course of RA, especially at an early stage of the disease, are often difficult to distinguish from other types of arthritis, including LA, since both diseases share similar symptoms. Currently, RA diagnosis is based on the detection of anti-citrullinated protein antibodies (ACPA), while LA is diagnosed based on antibody response to *B. burgdorferi,* estimated using ELISA and western blot analysis [3,4]. Although, antibodies against *B. burgdorferi* are not present in all patients with LA [1]. This is a significant clinical problem because the diagnosis determines treatment, which is different for both diseases. The early identification of patients in the preclinical phase of RA and LA is of high importance since early treatment can prevent joint damage. Thus, there is a strong need to identify additional diagnostic approaches allowing improved early diagnosis, as well as differentiation of RA from LA. This problem can be further complicated because it is highly possible that RA, as an autoimmune joint disease, may follow Lyme disease, as reported in a recent study [5].

Both RA and LA are characterized by inflammation in joints [2] that triggers generation of reactive oxygen species (ROS) [6] and promotes oxidative modifications of cellular macromolecules. It is well known that, as the essential building blocks of bio membranes, poly-unsaturated fatty acids (PUFAs) bound in phospholipid, are extremely vulnerable to ROS attack [6]. The ROS-mediated transformation of PUFAs yields various metabolites, including oxidative cyclization

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Abbreviations

ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
CRP	C-reactive protein
DAS	disease activity scores
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
ESI	electrospray ionization
HILIC	hydrophilic interaction liquid chromatography
HPLC	high performance liquid chromatography
LA	Lyme arthritis
LPC	lysophosphatidylcholine
LPE	lyso-hosphoethanolamine
PCA	principal component analysis
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PEO	ether-linked phosphoethanolamine
PI	phosphatidylinositol
PLA_2	phospholipase A_2
PLS-DA	partial least squares-discriminate analysis
PUFAs	polyunsaturated fatty acids
RA	rheumatoid arthritis
QTOF	quadrupole time of flight mass spectrometer
ROS	reactive oxygen species
SM	sphingomyelin
VAS	Visual Analog Scale
VIP	variable importance in projection

products such as isoprostanes and oxidative fragmentation products, including reactive aldehydes, an increased level of which we have observed in the course of RA and LA [7,8]. This indicates a strong relationship of PUFA modifications with the disease. However, insights into phospholipid metabolism in the course of both diseases are important, especially considering that changes in PUFA profiles can be associated with deviation in PL profiles, affecting their biological roles in membranes and in signaling. In addition, PUFA alterations play a crucial role in inflammatory processes [10].

Therefore, the aim of the study was to investigate the changes in plasma phospholipid profiles in both diseases that could help clarify mechanisms involved in RA and LA development. For this purpose, we used a lipidomic approach that allows not only identification of novel lipid signatures associated with these diseases, but may also help to identify some phospholipid species, indicating potential biomarkers for Lyme disease.

2. Materials and methods

2.1. Chemicals

All solvents used were of LC-MS grade. All chemicals were purchased from Sigma-Aldrich (Steinheim, Germany) and had greater than 95% purities. Phospholipid internal standards were purchased from Avanti Polar Lipids.

2.2. Biological material

Nine RA patients (three females and six males) with an average age of 48 years (range 23–79 years), nine LA patients (three females and six males) with an average age of 49 years (range 22–81 years), and nine healthy subjects (three females and six males), with an average age of 47 years (range 24–71 years) were enrolled in this study. From all the above patients, as well as from healthy people, blood was drawn into ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 2000 × g (4 °C) to obtain plasma. The LA, RA, and control plasma samples included in the study were collected in the Department of Infectious Diseases and Neuroinfections, and the Department of Rheumatology and Internal Diseases, Medical University of Bialystok (Poland). The study commenced after obtaining the approval from the Local Bioethics Committee Medical University of Bialystok (Poland), and written informed consent was obtained from all patients.

Diagnosis of RA was based on the criteria of the American College of Rheumatology (ACR) [11]. All patients with RA had a rheumatoid factor and ACPA present (5U/ml was considered as cut-off value). Their disease activity evaluation was based on the four parameters of disease activity scores C-reactive protein (DAS28-CRP) [12]. This index is based on the number of painful swollen joints, as well as on the assessment of disease activity indicated by the patient on the scale of 10 cm Visual Analog Scale (VAS) and CRP. While obtaining the disease history of each patient, particular attention was given to the current use of certain medications (anticoagulants and antiplatelet drugs) and comorbidities (liver, kidney or cardiovascular diseases, cancer, respiratory disorders, diabetes).

Diagnosis of LA was confirmed based on epidemiological anamnesis (92% of LA patients reported previous tick bites), clinical manifestation in large joints, including asymmetric inflammation, limited movement, and muscle pain. Serological test results for detection of anti-*B. burgdorferi* IgM and IgG antibodies in an enzyme-linked immunosorbent assay (ELISA) (*Borrelia* recombinant IgG and IgM High Sensitivity, Biomedica, Austria), were confirmed by western blot analysis. In all LA patients, IgM and/or IgG anti-*B. burgdorferi* antibodies were found in serum. The mean IgM anti-*B. burgdorferi* antibodies titer was 21 BBU/ml (minimum 11 BBU/ml, maximum 72 BBU/ml), and the mean IgG anti-*B. burgdorferi* antibodies titer was 36 BBU/ml (minimum 11 BBU/ml, maximum 79 BBU/ml). All patients with LA had negative serological test results typical for RA (Table 1).

The exclusion criteria for control and patient groups were as follows: pregnancy; lack of written consent; recent treatment with antibiotics, nonsteroidal anti-inflammatory drugs, or steroids. In the control group, no history of arthritis was observed. Patients and healthy subjects with a history of alcohol abuse or heavy smoking were also excluded from the study.

Another set of plasma samples (twenty five in each group) was used to quantify plasma level of LPE (14:0) by targeted analysis. Characterization of these groups of patients and healthy subjects are presented in the (Table 2).

Table 1
Results of blood laboratory tests of healthy subjects and patients with RA and LA.

	Healthy subjects n = 9	LA n = 9	RA n = 9
Age, years	47 (24–71)	49 (22–81)	48 (23–79)
Female, %	33,3	33,3	33,3
DAS-28	–	–	4,2 (3,8-8,2)
ESR, mm/h	6,8 (2,1–8,7)	37 (14–86)	36,6 (10–76)
CRP, mg/l	2,5 (0,2–9,1)	32 (2,1–152)	18,1 (2,4–98,6)
ACPA, U/ml	–	–	> 5
anti-*B.burgdorferi* IgM BBU/ml	–	21 (11–72)	–
anti-*B.burgdorferi* IgG BBU/ml	–	36 (11–79)	–

ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein, DAS, disease activity score; ESR, erythrocyte sedimentation rate.

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