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Original research article

Metabolites of arachidonic acid and linoleic acid in early stages of non-alcoholic fatty liver disease—A pilot study

Dominika Maciejewska[a], Piotr Ossowski[a], Arleta Drozd[a], Karina Ryterska[a], Dominika Jamioł-Milc[a], Marcin Banaszczak[a], Małgorzata Kaczorowska[a], Anna Sabinicz[a], Joanna Raszeja-Wyszomirska[b], Ewa Stachowska[a,*]

[a] Department of Biochemistry and Human Nutrition, Pomeranian Medical University, Szczecin, Poland
[b] Department of General, Transplant and Surgery of the Obser, Warszawa, Poland

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver conditions related to fat infiltration. The role of liver triacylglycerol accumulation in NAFLD is not fully understood.
Methods: Twenty-four patients, 12 in the first and 12 in the second stage of NAFLD, were prospectively enrolled in this study. Biochemical parameters and eicosanoids (HETE and HODE) were compared between the first and the second stage of hepatic steatosis and the effect of a 6-month dietary intervention on these parameters was evaluated. Eicosanoid profiles were extracted from 0.5 ml of plasma using solid-phase extraction RP-18 SPE columns. The HPLC separations were performed on a 1260 liquid chromatograph.
Results: Patients with stage I NAFLD had a significantly higher level of HDL cholesterol and a lower level of 5-HETE. Patients with grade II steatosis had higher concentrations of 9-HODE. Following the six-month dietary intervention, hepatic steatosis resolved completely in all patients. This resulted in a significant decrease in the concentrations of all eicosanoids (LX4, 16-HETE, 13-HODE, 9-HODE, 15-HETE, 12-HETE, 5-oxoETE, 5-HETE) and key biochemical parameters (BMI, insulin, HOMA-IR, liver enzymes).
Conclusion: A significant reduction in the analyzed eicosanoids and a parallel reduction in fatty liver confirmed the usefulness of HETE and HODE in the assessment of NAFLD.
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1. Introduction

Non-alcoholic fatty liver disease (NAFLD), which affects 20–30% of adults in developed countries, has emerged over the last two decades as an important clinical entity. In the United States almost 71 million individuals suffer from fatty liver disease, which is now the most common chronic liver condition in the country [1,2]. NAFLD, similar to the metabolic syndrome, is associated with dyslipidemia [3], cardiovascular disease, obesity [4], type II diabetes [4] and insulin resistance. The liver, which is an insulin sensitive organ, plays an important role in maintaining energy homeostasis [4].

Insulin resistance causes a lack of inhibition of gluconeogenesis and hyperglycemia. On the other hand, hyperinsulinemia stimulates increased hepatic synthesis of fatty acids and leads to steatosis [5]. The accumulation of triacylglycerols (TG) and rising oxidative stress induce the secretion of inflammatory mediators by hepatocytes, such as TNFα, interleukin-6, CRP protein, fetuin-A, and fibrinogen [6]. Increasing insulin resistance, lack of inhibition of TG accumulation and escalating inflammation may be the cause of the progression from simple liver steatosis to nonalcoholic steatohepatitis (NASH) [7].

Inflammation is a natural mechanism which protects the host from infection. During inflammation, chemoattractants are released and endothelial adhesion molecules are activated. Physiological mediators play an important role in host defense. When they are produced inappropriately, or in the wrong proportions, they can cause serious tissue damage. One of the key mediators of inflammation is produced by polyunsaturated fatty acids (PUFA), particularly by arachidonic acid (AA) and linoleic acid (LA) [1,8]. Lipoxygenase (LOX) and cyclooxygenase (COX) convert AA to eicosanoids, which are strong inflammatory modulators. This family includes prostaglandins (PG), leukotrienes (LT), lipoxins (LX),

* Corresponding author. Fax: +48 91 441 4807.
E-mail address: Polandewast@sci.pum.szczecin.pl (E. Stachowska).

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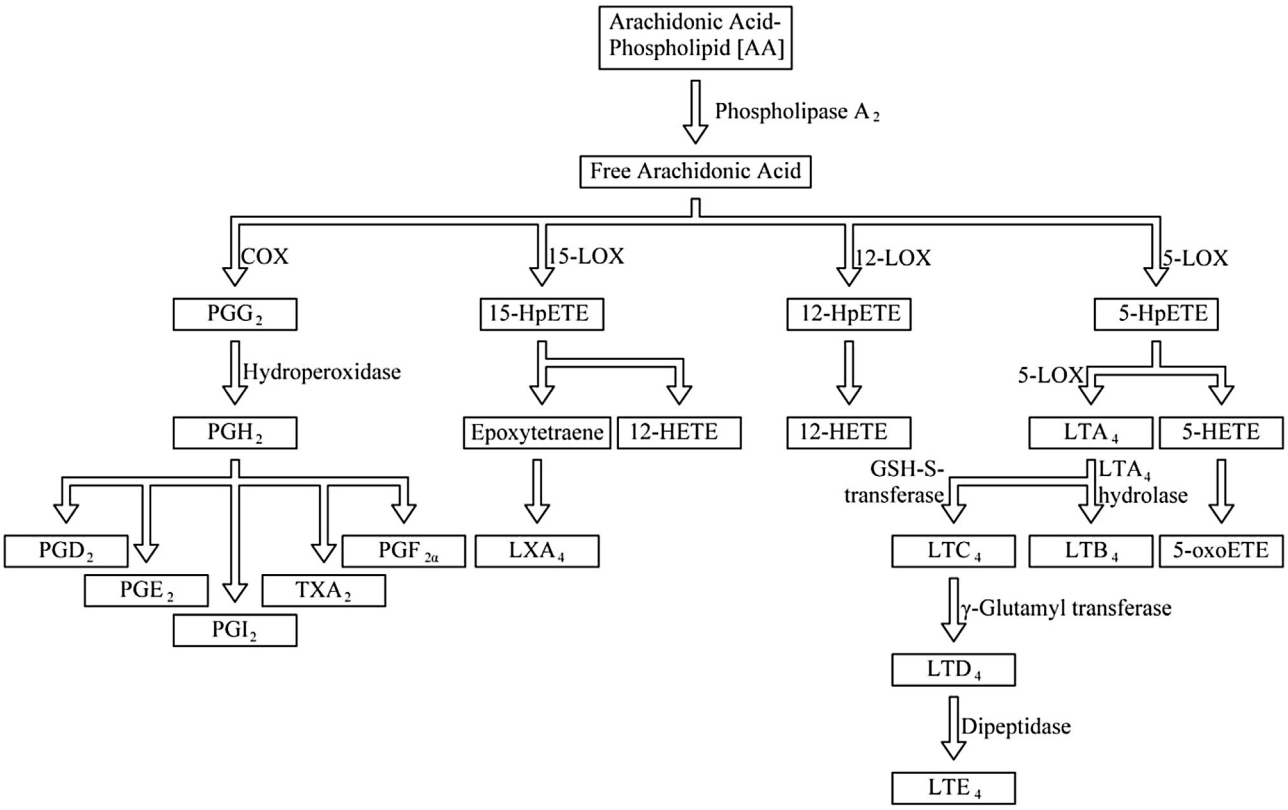

Fig. 1. Eicosanoides from arachidonic acid (AA).

hydroxyeicosatetraenoic acids (HETE) and hydroperoxyeicosatetraenoic acids (HpET) [9,10] (Fig. 1).

Linoleic acid is another type of acid that produces important inflammatory mediators. It is the precursor of all fatty acids from the omega 6 family. Its products, −9 and 13 hydroxyoctadecaenoic acids (9-HODE and 13-HODE), are markers of oxidative stress. They may arise during enzymatic conversion by the action of lipoxygenases or by oxidation of the non-enzymatic pathways [11] (Fig. 2).

2. Aim of study

The aim of this study was to compare the profile of eicosanoids (AA and LA derivatives) and biochemical parameters in patients with NAFLD. The differences in these parameters were compared between patients with stage I and II hepatic steatosis. We also compared differences in the eicosanoids profile following reduction in steatosis. A six-month dietary intervention was undertaken to achieve a reduction in fatty liver.

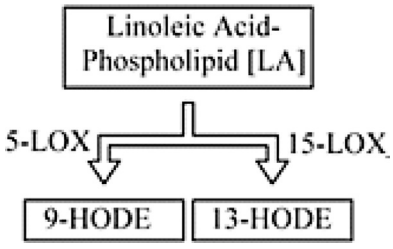

Fig. 2. Inflammatory mediators from linoleic acid (LA).

Table 1
Differences in eicosanoids between men and women.

Eicosanoids (ug/ml)	Woman $n = 10$		Man $n = 14$		*P* Value
	Median	IQR	Median	IQR	
LX A4	2.44	1.92	2.02	2.36	NS
16-HETE	0.21	0.06	0.20	0.15	NS
13-HODE	0.92	0.25	1.23	0.59	NS
9-HODE	0.71	0.30	0.74	0.41	NS
15-HETE	3.79	2.23	3.29	1.32	NS
12-HETE	6.39	7.32	4.92	2.18	NS
5-oxo ETE	1.07	0.23	1.98	0.93	NS
5-HETE	2.08	0.46	2.12	1.38	NS

3. Materials and methods

3.1. Study Plan

3.1.1. Patients

Twenty-four patients diagnosed with the early stages of NAFLD were enrolled in this study. In order to reduce the level of NAFLD, patients underwent a six-month dietary intervention. All patients were negative for HBsV and anti-HCV (hepatitis C virus) and had a negative history of alcohol intake (less than 20 g/d). In addition, the patients did not take any medication before and during the study which significantly affected glucose and lipid metabolism (fibrates, statins, NSAIDS, corticoids, metformin). The study protocol was approved by the ethics committee of Pomeranian Medical University (Szczecin, Poland) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The patients were divided into two groups with reference to the stage of NAFLD (stage I—12 patients, stage II—12 patients). There were no significant differences in eicosanoids between men and women (Table 1). Therefore, we decided to consider these two groups together.

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