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Research Article

Correlation between several extrinsic factors and Paraoxonase 1 activities

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Abstract. Objective: to investigate the PON1 activity (aryl esterase, paraoxonase and lactonase) as well as the possible influence of non-genetic factors in a representative cohort of patients with steatosis. Material and methods: We enrolled 39 subjects with steatosis that were hospitalised for multidisciplinary evaluation. The control group comprised 60 subjects without steatosis present at ultrasonography. Both groups were matched for age and sex. Each study participant answered a questionnaire regarding their lifestyle, comprising questions about diet, physical activity performed, use of medications, drugs or tobacco. We determined paraoxonase activities for all subjects. Results: There were no differences regarding paraoxonase activities between patients with steatosis as compared with healthy subjects. We did not get any statistical significance in the analysis of all studied extrinsic factor in relation to paraoxonase activities. Conclusion: steatosis and diet did not influenced paraoxonase activities.

Key Words: steatosis, paraoxonase activities, extrinsec factors.

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Introduction

Non-alcoholic fatty liver disease represents a large spectrum of conditions which ranges from steatosis, that generally has a benign, nonprogressive evolution, to non-alcoholic steatosis, a form which can develop into cirrhosis and hepatic cancer (Adams *et al* 2011; Samy *et al* 2011; Lee 2011; Younossi *et al* 2012; Li *et al* 2012). The cause that leads to fatty non-alcoholic liver resides in the accumulation of triglycerides in the liver, (Zimmermann *et al* 2011; Samy *et al* 2011; Ndumele *et al* 2011; Grdic Rajkovic *et al* 2011), that represents the source of oxidative stress and promote the inflammatory process.

Human plasmatic Paraoxonase 1 (PON1), which is encoded by a gene found on the long arm of chromosome 7 q21.3 (La Du 1996; She *et al* 2012), is a esterase/lactase which is associated with high density lipoproteins (HDL) which contain apolipoprotein J (clusterin) and apolipoprotein A (Bełtowski *et al* 2003; Audikovszky *et al* 2007; Çakatay *et al* 2008). PON1 is associated to HDL hydrolyseparaoxon, organophosphorus compounds, unsaturated aliphatic esters, carboxylic aromatic esters (Costa *et al* 2003; Aviram *et al* 2004; Soran *et al* 2009; Kedage *et al* 2010; James *et al* 2010).

Reduced values of PON1 activity were associated to diseases that have oxidative lesions and lipid peroxidation (Costa *et al* 2005; Bhattacharyya *et al* 2008; Camps *et al* 2009) and also, at an individual level show large variations of enzymatic activity, genetic factors explaining only in part these variations.

After recent studies demonstrated that the native PON1 activity is that of a lactonase (Khersonsky *et al* 2005; Aharoni *et al* 2005; Khersonsky *et al* 2006) while the previously intensive studied arylesterase and paraoxonase activities, are unexpected, a correct evaluation of PON1 activity implies the evaluation of all three activities: arylesterase, paraoxonase and lactonase. Although many studies focused on it, the results are controversial with regards to the effect of hypolipidemic drugs on PON1: some have demonstrated an increase in PON1 activity, while others could only demonstrate an improvement of the lipid profile (Costa *et al* 2005).

Similar to the oral antidiabetics (She *et al* 2012), aspirin seems to increase the activity of PON1 (Costa *et al* 2005), but other studies although claim an amelioration of the enzymatic activity, underline the fact this happens only to coronary patients (She *et al* 2012).

While the data concerning alcohol consumption and PON1 are inconsistent and in the same time dose dependant (van der Gaag *et al* 1999; Sierksma *et al* 2002; Rao *et al* 2003; Sarandol *et al* 2003), cigarette smoke reduces irreversibly the plasmatic levels of the enzyme (Nishio *et al* 1997; She *et al* 2012).

The pomegranate juice amplifies PON1 activity (Costa *et al* 2005, She *et al* 2012). Regarding the intake of vitamin C, the available data is inconsistent (Costa *et al* 2005; She *et al* 2012). Also a diet rich in triolein, olive oil or oleic acid increases the activity of plasmatic PON1, while olineic acid reduces it (Costa *et al* 2005).

It is accepted unanimously that constant physical exercises increases the activity of PON1 (Costa *et al* 2005; She *et al* 2012). The objective of the current study was to investigate the PON1 activity (aryl esterase, paraoxonase and lactonase) as well as the possible influence of non-genetic factors in a representative cohort of patients with steatosis.

Materials and methods

Participants

We enrolled 39 subjects with steatosis that were hospitalised for multidisciplinary evaluation. The control group comprised 60 subjects without steatosis present at ultrasonography.

Both groups were balanced regarding age: 55.38±12.59 years in the steatosis group, respectively55.11±12.64 years(p=0.9) in the control group, and sex (35.5% men with steatosis, 38.2% healthy men, p=0.8).

The diagnosis of steatosis was established based on ultrasound examination

Prior to the enrolment in the study, all the participants were explained the stages and objectives of this study. Written consent was obtained from each participant and the study was approved by the Ethics Committee. The consent and the research protocols were in agreement with the Helsinki Declaration of World Medical Association.

We excluded from our study patients that presented medical evidences of any pathology that may influenced PON1 activity: liver damage (acute or chronic viral hepatitis), declared alcohol intake (>20g/day – men, >10g/day – women) in the past 6 months, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alpha-1antitrypsin deficiency, hemochromatosis, porphyria, Budd-Chiari syndrome, hepatic cirrhosis, inflammatory diseases like infections, psychiatric disorders which influence the values of PON1, malignancies, renal diseases.

Anthropometric measurementsandclinical examination

For each participant we recorded general data (age,sex, area of origin), clinical and laboratory data. Information about the presence of comorbidities: hypertension, heart failure, type 2 diabetes, cancer, stroke, coronary heart disease or angina were collected from an medical history and clinical examination.

To exclude the influence of demographic data on the enzyme activity, the participants in this study belonged to the same geographical areas. All had their height, weight and waist circumference measured.

Also, each study participant answered a questionnaire regarding their lifestyle, comprising questions about diet, physical activity performed, use of medications, drugs or tobacco.

To measure the height, the subjects were seated in the upright position, without shoes and using a measuring rod. There were three determinations carried out and the arithmetic mean of these measurements in meters was recorded.

Also in the standing position, the abdominal circumference of each subject was determined using a flexible strip chart recorder. There have been three consecutive measurements with patients in maximum exhale, midway between the umbilicus and xiphoid appendix. The mean value of these determinations, expressed in centimetres, has been reported (O'Riordan *et al* 2009).

We calculated body mass index(BMI, kg/m^2) by applying the equation: weight (in kilograms) divided by the height (in square meters). To assess the weight, study participants were lightly dressed (they had no shoes and wore only light clothing) in this way the maximum margin of error was of+ /-50 g. We assessed body mass index (BMI, kg/m²) as follows: normal<25kg/m², overweight - BMI between 25 and 30 kg/m², obesity grade I - BMI between 30.1 and 34.9 kg/m²; Grade II - BMI between 35 and 40kg /m², grade III - BMI> 40 kg/m²) (WHO 2000).

Blood and serum samples

All subjects included in the study followed a 12-hour fasted overnight and the next morning blood samples were collected from the ulnar vein using vacutainers without anticoagulant. These samples were immediately refrigerated at 4^{0}C. We then prepared samples for serum enzyme determinations, which we obtained by centrifuging blood (3 min at 3000 rpm). Subsequently they were frozen at-80^0 C and kept under these conditions until they were analysed.

Paraoxonase activities

According to Eckerson et al (1983), with minor modifications, we determined the PON1 activities (paraoxonase, aryl esterase and lactonase) by spectrophotometric methods in the heparinized plasma. To determine the paraoxonase activity paraoxonwas used (O, O- diethyl -Op - nitrophenylphosphate, Sigma Chemical co. Seelze, Germany). The sample contained a basic mixture made up of 1.0 mM of paraoxon, 2MNaCl and 1 mMCaCl2 in 50 mM glycine - NaOH buffer (pH 10.5). By adding the plasma samples we initiated the reaction, and absorption was monitored for 90 sec at 405 nm. Using phenylacetate (Sigma Chemical Co., Steinheim, Germany) 1 mM in 20 mMTris- HCl (pH) that contained 1 mMCaCl2, we measured the aryl esterase and lactonase activity of PON. The rate of phenylacetate hydrolysis at 25^{0}C was measured together with the increase in absorbance at 270 nm for 90 seconds. At the same time, a control sample, which had the same content but without the plasma, was run simultaneously for some corrections for spontaneous decomposition of the substrate activity for both activity determinations. All samples were run in duplicate. Obtained data was expressed in U/l for paraoxonase activity of PON1 (paraoxonase nanomoles hydrolyzed per minute) and kU/l for arilesterase activity of PON1 (phenylacetate micromoles hydrolyzed per minute).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 20. Nominal variables were described using frequencies and continuous variables and were described by mean and standard deviation, or by median and percentiles (25-75%). Kolmogorov-Smirnov test for normality of distribution was performed for all continuous variables. Chi-square test was used in order to compare the frequencies of nominal variables. Differences between groups regarding continuous variables were examined using the t test and Mann-Whitney test. To evaluate differences between groups with more than 2 categories concerning continuous variables we used ANOVA and Kruskal-Wallis.The correlation between two continuous variables was assessed using Pearson correlation or Spearman's rho. All tests were chosen taking into account the normality of the distribution. The level of statistical significance was set at p<0.05.

Results

Clinical and demographic characteristics and laboratory findings of patients in the two groups are presented in Table 1.

Table 1. Clinical and demographic characteristics and laboratory findings of patients in the two groups

Variable		Subjects without steatosis (n=60)	Patients with steatosis (n=39)	p
Age (yr)		56.75±11.96	55.9±11.92	0.7
Sex	**Men**	26 (43.3%)	19 (48.7%)	0.7
	Women	34 (56.7%)	20 (51.3%)	
A-ase (U/mL)		67.96±19.47	62.62±16.47	0.1
L-ase (µmoli/L)		57.32±15.15	58.16±16.75	0.7
P-ase (U/l)		274.5 (164;484.7)	222 (136; 492)	0.2
Total cholesterol (mg/dl)		220.88±54.77	206.59±47.9	0.1
HDL-C (mg/dl)		51.07±12.69	47.03±10.45	0.1
Triglycerides (mg/dl)		121 (94.2;164.5)	159.5 (112.5; 208)	0.05
Glycaemia (mg/dl)		92.8±15.4	119.4±48.52	0.002
BMI		26.31±4.8	32.01±3.9	<0.001
Waist circumference		93.15±14.22	112.05±13.14	<0.001
Diabetes mellitus		15 (25%)	26 (66.7%)	<0.001
Hypertension		24 (40%)	31 (79.5%)	<0.001
Lipid-lowering medication		12 (20%)	20 (51.3%)	0.002

We determined the existence of a weak inverse correlation between waist circumference values and A-ase (r=-0.2, p=0.009). HDL-C and TC variables had a strong, and respectively medium, influence on A-ase levels (r=0.5, p <0.001, r=0.34, p=0.001). We have established a medium correlation between the values of HDL-C and L-ase (r=0.3, p=0.002) and between CT values and P-ase (r=0.31, p=0.002). We did not find a correlation between age and P-ase, A-ase or L-ase (r=-0.1, p=0.2, r=-0.09, p=0.3, r=-0.09, p=0.3). The patients sex had nosignificant influence on P-ase, A-ase or L-ase (p=0.9, p=0.3 , respectively p=0.3). We found no correlation between BMI, glucose, TG and values of these three enzymes.

Smoking had a significant influence on the values of A-ase (p=0.04) and alcohol on P-ase values (p=0.002) .

We obtained a value close to the threshold of 0.05, when analysing the relationship between effort, sausage consumption and P-ase values (p=0.08, p=0.06 respectively). We found a similar situation when assessing the relationship between meat consumption and L-ase values (p=0.07).

We did not get any statistical significance in the analysis of all the other variables in relation to A-ase, L-ase and P-ase.

The influence of various life style factors are shown in Table 2.

Table 2. Comparison between groups regardin life style factors

Variable		Subjects without steatosis (n=60)	Pacients with steatosis (n=39)	p
Smoking		14 (23.3%)	6 (15.4%)	0.4
With a history of smoking		11 (18.3%)	10 (25.6%)	0.5
Alcohol		6 (10%)	6 (15.4%)	0.4
Vegetable oils		47 (78.3%)	33 (84.6%)	0.6
Nuts		11 (18.3%)	6 (15.4%)	0.9
Fish		11 (18.3%)	3 (7.7%)	0.2
Physical effort		44 (73.3%)	30 (76.9%)	0.8
Fruits, vegetables	More than once a day	1 (1.7%)	-	0.4
	Once a day	41 (68.3%)	31 (79.5%)	
	Not every day	13 (21.7%)	7 (17.9%)	
	Rare	5 (8.3%)	1 (2.6%)	
Fried oil	Predominant	15 (25%)	14 (35.9%)	0.8
	Moderate	14 (23.3%)	7 (17.9%)	
	Rarely	12 (20%)	7 (17.9%)	
	Never	13 (21.7%)	8 (20.5%)	
Meat	More than once a day	7 (11.7%)	6 (15.4%)	0.02
	Once a day	11 (18.3%)	14 (35.9%)	
	Not every day	32 (53.3%)	19 (48.7%)	
	Rare	10 (16.7%)	-	
Type of meat	More red meat	11 (18.3%)	12 (30.8%)	0.1
	Equally	34 (56.7%)	15 (38.5%)	
	More white meat	6 (10%)	8 (20.5%)	
	Not at all	9 (15%)	4 (10.3%)	
Sausages	More than once a day	3 (5%)	1 (2.6%)	0.5
	Once a day	2 (3.3%)	4 (10.3%)	
	Not every day	23 (38.3%)	15 (38.5%)	
	Rare	32 (53.3%)	19 (48.7%)	
Fast-food	Frequently	48 (80%)	27 (69.2%)	0.3
	Rare	12 (20%)	12 (30.8%)	
Sweets	More than once a day	6 (10%)	3 (7.7%)	0.1
	Once a day	1 (1.7%)	4 (10.3%)	
	Not every day	24 (40%)	10 (25.6%)	
	Rare	29 (48.3%)	22 (56.4%)	

Discussions and conclusions

Non-alcoholic fatty liver disease, the most common liver abnormality in the developed world, described recently as part

of the metabolic syndrome (Marchesini *et al* 2001; Farrel *et al* 2006; Bajaj *et al* 2009; Oh *et al* 2011; Ndumele *et al* 2011; Younossi *et al* 2012), is one of the main causes of chronic liver disease. Along with type 2 diabetes, obesity or overweight, its prevalence has increased substantially (Aslan *et al* 2008) and it is increasing in Western countries, affecting approximately 20-30 % of the population (McCullough *et al* 2005; Farrell *et al* 2006; Yilmaz *et al* 2012; Younossi *et al* 2012).

The mechanism of liver injury is explained by the release of free fatty acids (FFA) from adipose tissue deposits into the portal circulation (Rodríguez-Hernández *et al* 2011) and an increased concentration of unsaturated FFA in the liver may lead to steatosis, considered the first blow to the liver (Samy *et al* 2011). Currently no common imaging technique (ultrasound) is able to detect minimal histological changes of inflammation and ballooning, so thathepatic steatosis, non-alcoholic steatosis or other alcohol-induced chronic liver diseases can be differentiated, because of thesimilar histological appearance (Samy *et al* 2011; Younossi *et al* 2012).

Although liver biopsy, and proton magnetic resonance spectroscopy (H-MRS) are considered the golden standard methods for quantification of fat deposits in the liver, recent studies indicate the effectiveness of ultrasound in the assessment of hepatic steatosis (Martín-Rodríguez *et al* 2013).

Recently it has been suggested that PON1 activities associated with HDL are implicated in pathogenesis of metabolic syndrome by demonstrating the existence of reduced PON 1 activities in this syndrome (Aviram *et al* 1998; Ferretti *et al* 2005; Kotani *et al* 2009). The influence of different factors such as food, lifestyle, dietary habits or certain drugs, on PON1 activity have also been reported. In this study we aimed to investigate the PON1 activities (arylesterase, paraoxonase and lactonase) and the possible influence of lifestyle in a representative cohort of subjects with hepatic steatosis.

This was the first study from Romania to investigate the PON1 activity in patients with hepatic steatosis and to evaluate a possible association of some lifestyle factors on enzyme activity.

In this study, we observed statistically significant differences between the 2 groups for triglycerides, glucose, BMI, waist circumference, diabetes, hypertension and lipid-lowering medication, the data obtained are consistent with the results of other studies (Ndumele *et al* 2011). In disagreement with our expectations, we did not obtain significant differences between the two groups of participants for total cholesterol and HDL, which could be explained by statistically significant differences in the use of lipid-lowering medication, which may be responsible for these results.

We obtained no difference between groups in terms of PON1 enzyme activities similar with other researchers (Tabur *et al* 2010), although other reportshave shown low values of their pathologies involving oxidative stress (Kotani *et al* 2009). Hepatic steatosis is the first hepatic change and it was speculated that this context lipotoxicity would be on the forefront, to an extent more important than insulin resistance (Bajaj *et al* 2009). In these circumstances the changes can only be in the RNA enzyme and because of the longer half-life of PON1 they cannot be detected at this stage of liver damage. The alterations ofenzymatic activities will appear later (Feingold *et al* 1998). We observed an inverse correlation between the arylesterase activity, namely the enzyme bioavailability values, and the waist circumference, and a direct correlation with HDL-C and TC, in agreement with data from other studies (Tabur *et al* 2010). Lactonase activity was positively correlated and we observed a weak association with HDL-C, similar to studies that have shown association only with certain subtractionof HDL (Grdic Rajkovic *et al* 2011) while, contrary to our expectations, P-ase activity was weakly associated only with CT values. These results could be explained by the small number of participants in the study or because of PON1 catalytic inactivity (assessed by P-ase activity)present at this stage of liver disease.

Like other studies, we observed no influence of sex (Costa *et al* 2005) on enzyme activities. We found no correlation between PON1 activity and blood glucose, triglycerides, BMI, the data so far being controversial (She *et al* 2012). These discrepancies are explained by the genetic variability of different groups investigated.

Among lifestyle factors, smoking had a significant influence on the values of A-ase, as in other reports (Costa *et al* 2005; She *et al* 2012), and this is probably linked to reactive aldehyde. P-ase activity was influenced by alcohol intake in agreement with other publications (Costa *et al* 2005, She *et al* 2012). There are no genetic polymorphisms of the PON1 that modulate the activity in relation to the dose of alcohol consumption, but changes in enzyme activity, that have an effect on protein-kinase C. This kinase is important for the phosphorylation of an active site (Sp1) in the promoter region of the PON1 gene (Costa *et al* 2005).

Close values to statistical significance threshold were obtained when analysing the relationship between exercise, eating sausage and P-ase values, as in other studies (Costa *et al* 2005; She *et al* 2012).

Similarly, when analyzing the relationship between meat consumption and L-ase values, the data obtained was close to statistical significance probably because of the small number of subjects that participated in the study. Meat consumption probably validates PON1 antioxidant function, assessed by L-ase values. In other cases, the lack of statistical significance may be due to the small number of participants in the study. On the other hand, it should be considered that the data obtained was based on the honesty of the participants in the study and therefore the accuracy of reported data could not be assessed.

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