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## Research paper

## Oxidative stress influence on renal dysfunction in patients with obstructive jaundice: A case and control prospective study

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## ABSTRACT

**Background:** Obstructive Jaundice (OJ) is associated with a significant risk of developing acute renal failure (ARF). The involvement of oxidative stress in the development of cholestasis has been demonstrated in different experimental models. However, its role in the morbidity of human cholestasis is far to be elucidated. The aim of the study was the evaluation of oxidative stress markers in blood from patients with OJ and its relation to complications and benign/malignant evolution of cholestasis. **Methods:** A prospective cross-sectional study of 105 patients with OJ and 34 control subjects were included. Several markers of liver function and oxidative stress, such as lipoperoxides (LPO), as well as reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities were assessed. **Results:** The patients with OJ showed a marked increase in plasma levels of LPO, SOD and GSH, while GSH-Px levels were decreased. The increase in lipid peroxidation products and the depletion of SOD activity in blood were also related to renal dysfunction. The highest level of LPO was associated with malignant etiology of the disease. The logistic regression analysis showed that the age of the patient and the levels of LPO in blood were predictors of renal dysfunction in OJ patients. **Conclusions:** This study demonstrates a correlation between oxidative stress and renal dysfunction patients with OJ.

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## 1. Introduction

The obstruction of extrahepatic biliary tract results in the dilatation of bile ducts with an accumulation of hydrophobic bile acids in hepatocytes. The toxic biliary products, such as glycochenodeoxycholate, as well as neutrophil migration promote the generation of oxygen-free radicals, unbalancing antioxidant status in the hepatic parenchyma [1]. Exogenous regulation of oxidative stress ameliorates liver injury induced by experimental cholestasis [2–4]. The pathogenesis of OJ involves a systemic alteration that affects different extrahepatic tissues. An increase in lipoperoxidation products is observed in extrahepatic tissues, including kidney and brain, in animals subjected to OJ [5,6].

Acute renal failure is a significant adverse outcome of OJ, observing rates of 6–18% [7], and is associated with a significant morbidity and postoperative mortality [8,9]. The administration of melatonin reduces lipid oxidation in kidney during experimental OJ [10]. Hypotension and sepsis, secondary to depletion of extracellular fluid and myocardial dysfunction has proven to be relevant in the development of kidney disease in cholestatic patients [11–19]. However, the role of oxidative stress during renal complications of OJ has not been studied in detail.

The main objective of the present study was to assess the correlation between the alteration of oxidative stress biomarkers in blood and the presence of renal failure in patients with OJ.

## 2. Methods

## 2.1. Design of study

The study was designed as a prospective cross-sectional observational study. 105 patients with OJ were enrolled and

*Abbreviations:* OJ, obstructive jaundice; ARF, acute renal failure; LPO, lipoperoxides; GSH, reduced glutathione; CAT, catalase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDRD, modification of diet in renal disease; GFR, glomerular filtration rate; MDA, malondialdehyde; AP, alkaline phosphatase

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compared with 34 healthy subjects, matched by sex, age, weight, height, and body mass index. The patients were included over a period of 26 months. Inclusion criteria were OJ of benign or malign ethiology, levels of conjugated bilirubin higher than 2 mg/dl or total bilirubin higher than 3 mg/dl, biochemical cholestatic pattern, ultrasound evidence of extrahepatic bile duct dilatation higher than 12 mm and intrahepatic higher than 4 mm. Exclusion criteria were acute cholangitis, parenchymal liver disease, gastrointestinal hemorrhage, prior or concomitant intravenous fluid therapy, heart failure or chronic renal failure, undernourished patients, and treatment with diuretics, antihypertensives, cimetidine or trimethoprim. Informed consent was obtained from all participants.

The study was approved by the Ethical Committee for Clinical Research of the Institution.

## 2.2. Biochemical measurements

Biochemical and oxidative stress parameters were measured on patients peripheral blood samples while admission to hospital. Same determinations were performed in control subjects under similar conditions to baseline measurements in patients with obstructive jaundice. The levels of direct and total bilirubin, sodium, potassium, AST, ALT, alkaline phosphatase (AP), albumin and total protein were performed with Cobas Integra Roche-400 analyzer (Roche Diagnostics Ltd., Switzerland). Renal function was estimated by the modified formula known as MDRD (Modification of Diet in Renal Disease) [20]. Renal impairment was considered when the glomerular filtration rate (GFR) value was  $\leq 70$  ml/min ( $1.73 \text{ m}^2$ ). GFR was measured according to the MDRD using the following the formula:

$$\text{MDRD} = 186 \times [\text{creatinine, mg/dl}]^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ in women}) \times (1.212 \text{ if black population})$$

## 2.3. Oxidative stress markers

The markers of oxidative stress were assessed in plasma obtained after blood centrifugation at 3000 g for 5 min at 4 °C. Samples were stored at 80 °C until measurements.

LPO and GSH were determined using commercial assays (LPO-586 and GSH-400, Bioxytech SA, Oxis International, Portland, OR, USA). CAT and SOD were measured according to Aebi [21] and Sun [22] methods, respectively. GSH-Px was measured according to Flohe and Gunzler [23] method. The values were measured using a plate reader spectrophotometer Shimadzu UV-1603 (Shimadzu, Kyoto, Japan).

## 2.4. Statistical analysis

Results are expressed as mean  $\pm$  standard deviation (SD). Comparisons between two groups were performed using Student's t test for unpaired groups or Mann–Whitney. Comparisons between three groups were performed using ANOVA analysis followed of post-hoc Kruskal–Wallis test. Comparisons between proportions were performed by chi-squared test. Correlations of variables were evaluated with Pearson coefficient or Spearman rho coefficient. Multivariate analysis was performed to identify factors associated with renal dysfunction. The main variables considered were: etiology of jaundice, age, duration of jaundice, bilirubin, sodium, potassium, AST, ALT, AP, albumin, total protein, LPO, GSH, GSH-Px, SOD, CAT. Linear and logistic regression were performed with the estimated renal function by MDRD. Stepwise method was used excluding variables with  $P \geq 0.15$  (Student's t statistic for linear regression and Wald statistic for logistic regression).

## 3. Results

### 3.1. Oxidative stress in patients with OJ. Correlation with renal insufficiency

Table 1 shows general demographic and biochemical characteristics of the Control and OJ groups. OJ patients ( $n=105$ ) were distributed in 67 men (64%) and 38 women (36%), with mean age of  $69 \pm 12.8$  years old (15–93 years) (Table 1). The levels of peripheral LPO, GSH and SOD concentration were significantly higher in the group of patients with OJ compared to control subjects ( $p=0.0001$ ) (Table 1). By contrast, levels of GSH-Px showed a significant decline ( $p=0.0001$ ) (Table 1).

A strong positive correlation was found between levels of conjugated bilirubin and LPO in plasma ( $r=0.744$ ,  $p=0.0001$ ) (Fig. 1).

The creatinine clearance in control subjects ( $98 \pm 31.1$ ) was significantly higher than in OJ patients of benign ethiology ( $56 \pm 25.9$ ,  $p=0.031$ ). There were no statistically significant differences with creatinine clearance in patients with malign ethiology ( $72 \pm 35.2$ ,  $p=0.199$ ). The GFR of control subjects ( $104 \pm 38.2$  ml/min) was higher than in OJ patients of benign ethiology ( $84 \pm 37.9$  ml/min,  $p=0.010$ ) with a moderate non statistically significant improvement in the malign ethiology ( $116 \pm 93.3$  ml/min,  $p=0.184$ ). Renal failure was present in 32% of the patients, whereas it was only observed in 6% of controls. The presence of renal insufficiency in patients with OJ was associated with higher levels of total bilirubin ( $p=0.002$ ), as well as an increase in serum levels of LPO ( $p=0.017$ ) and GSH ( $p=0.017$ ) (Table 2). By contrast, the levels of SOD showed a decrease in patients with renal impairment ( $p=0.044$ ) (Table 2). There were no statistically significant differences in the levels of GSH-Px and CAT levels (Table 2).

A weak negative correlation was found between plasma levels of LPO and the GFR ( $r=-0.303$ ,  $p=0.001$ ) (Fig. 2).

### 3.2. Analysis of patients with OJ according to the benign/malign ethiology

There were not significant differences among the percentage of gender (men) in patients with benign ( $n=33$ , 31.5%) and malign ( $n=72$ , 68.5%) cholestasis (Table 3). The increased levels of total ( $20 \pm 11.5$  vs  $12 \pm 7.4$ ,  $p=0.0001$ ) and direct bilirubin ( $16 \pm 9.6$  vs  $9 \pm 6.0$ ,  $p=0.0001$ ), and AP ( $757 \pm 554.3$  vs  $528 \pm 577.3$ ,  $p=0.005$ ) in blood from patients with OJ of malign vs benign etiologies respectively, was probably due to the longer evolution period of the disease (mean duration for jaundice 18 vs 9 days) (Table 3). LPO levels were also higher in malignant etiology group. ( $603 \pm 202.0$  vs  $473 \pm 144.8$  nmol/l) ( $p=0.0001$ ) (Table 3).

### 3.3. Multiple linear regression analysis

Different variables such as age, duration of jaundice, bilirubin, sodium, potassium, AST, ALT, albumin, total proteins, GSH, SOD and CAT were eliminated from the model using the multiple F partial test ( $F=-0.2764$ ,  $p=0.735$ ; freedom degree=12.53). The multiple linear regression analysis for GFR estimated by the MDRD formula fulfilled the conditions of proper application such as linearity of independent variables, no co-linearity and independence among them, normality of residues and homoscedasticity of variances.

The linear adjusted equation for the GFR in OJ patients was:

**Table 1**  
Demographic characteristics and biochemical parameters of the cohorts.

	Control	Jaundiced	p*
Gender (% men)	64%	71%	0.607
Age (years)	57 ± 16.5	69 ± 12.8	0.001
Weight (Kg)	73 ± 13.9	73.3 ± 17.5	0.839
Height (cm)	162 ± 9.4	161 ± 15	0.923
Systolic blood pressure (mmHg)	122 ± 12.8	122.3 ± 20	0.730
Diastolic blood pressure (mmHg)	73 ± 10.6	70 ± 11.9	0.224
Temperature (°C)	37 ± 0.5	36 ± 0.4	0.634
Total Bilirubin (mg/dl)	0.500 ± 0.2	17.5 ± 11.00	0.001
Direct Bilirubin (mg/dl)	0.230 ± 0.21	13.9 ± 9.25	0.001
AP(U/L)	66 ± 27.1	684 ± 569.2	0.001
GGT (U/L)	68 ± 106.6	669 ± 537.5	0.001
LPO (nmol/L)	163 ± 82.8	563 ± 195	0.001
GSH (nmol/L)	1.80 ± 1.000	10.7 ± 5.3	0.001
GSH-Px (U/L)	22.8 ± 8.50	15.1 ± 11.80	0.001
SOD (U/L)	15.1 ± 11.100	168 ± 95.0	0.001
CAT (U/L)	3.8 ± 2.10	4.8 ± 4.90	0.124

\* Level of statistical significance obtained with Student's *t* test or Mann-Whitney, as appropriate.

$$\text{MDRD} = 67.74 + [29.57 \text{ if benign etiology}] \\ + [77.06 \text{ if malignant etiology}] - (AP \cdot 0.03) - (0.07 \cdot \text{LPO}) \\ + (2.22 \cdot \text{GSH-Px})$$

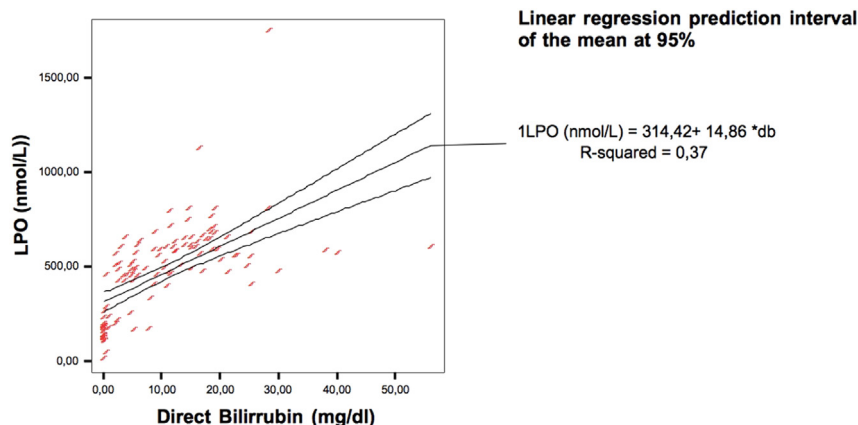
The adjusted coefficient of determination (R<sup>2</sup>) was 0.171, and F value was 5.485 ( $p=0.0001$ ). The statistical associative model indicated that 1 nmol/L increase of LPO will decrease MDRD estimation in 0.07 ml/min (IC95=0.01). In addition, 1 U/L increase of GSH-Px will increase MDRD estimation in 2.2 ml/min (IC95=1.1).

#### 3.4. Logistic regression analysis

Different variables (etiology, duration of jaundice, bilirubin, sodium, potassium, AST, ALT, AP, albumin, total proteins, GSH, GSH-Px, SOD and CAT) were eliminated from the model. The logistic regression analysis demonstrated that risk factors for renal dysfunction followed the equation:

$$Z = -5.791 + 0.044(\text{age}) + 0.003(\text{LPO})$$

The value of the likelihood ratio test was 12.532 ( $p=0.002$ ) and Hosmer–Lemeshow C value was 5.604 ( $p=0.691$ ). The statistical associative model indicated that the risk of renal dysfunction measured by MDRD was 1.05 times higher each year of age (5% risk increase per year). Moreover, for every increase of 10 units of LPO, the risk of renal dysfunction was 1.031 times greater (3% risk increase).



**Fig. 1.** Correlation between serum bilirubin and LPO concentration in blood from patients with OJ.

**Table 2**  
Direct bilirubin and oxidative stress parameters in blood from patients with OJ according to renal function.

	Normal** Function GFR ≥ 70 (ml/min)	Impairment** GFR < 70 (ml/min)	p*
Direct Bilirubin (mg/dL)	8.91 (9–12)	14.53 (10–24)	0.002
LPO (nmol/L)	428.76 (46–211)	588.03 (79–289)	0.017
GSH (nmol/L)	7.67 (5–60)	11.01 (5–71)	0.012
GSH-Px (U/L)	17.53 (12–88)	14.78 (5–15)	0.497
SOD (U/L)	145.48 (62–488)	99.74 (58–196)	0.044
CAT (U/L)	4.75 (5–16)	3.96 (2–90)	0.541

\*\* The results were expressed with the median and the range values in parenthesis.

\* Level of statistical significance obtained with Student's *t* test or Mann-Whitney, as appropriate.

#### 4. Discussion

Redox imbalance associated with OJ has been extensively demonstrated in experimental animal models [24,25]. However, there is a significant lack of evidence for this association in humans. Assimakopoulos et al. showed an alteration of oxidative status in intestinal tissue that may underlie the systemic endotoxemia in OJ patients [6]. Montilla et al. showed an exacerbation of hepatic lipoperoxidation with reduction of antioxidant status induced by ligation of extra-hepatic biliary duct in rats [3]. The present study demonstrated that lipoperoxidation markers in blood are increased in patients with OJ in relation to the renal dysfunction and the benign or malign etiology.

The neoplastic origin of the OJ was related to a longer evolution of the disease than that observed in the benign cholestatic etiology. In concordance with previous studies [26–29], the progression of the disease was related to the progression of markers of cholestasis (Table 3).

The evidences for the correlation between oxidative stress, renal dysfunction and progression of OJ were reinforced in the present study. We observed a drastic reduction of renal function in patients with OJ of benign origin with a mild not significant recovery in patients with malignant etiology. Overall, renal failure was present in 32% of the patients, whereas it was only observed in 6% of control subjects. A previous clinical study had reported a 10% renal dysfunction not related to the etiology in a cohort of 55 patients with OJ [30]. This higher rate in our study was probably related to the use of higher threshold for considering renal insufficiency (GFR less than 70 ml/min instead of 50 ml/min), the election of a more accurate method to measure kidney function, increased number of patients and their distribution according to

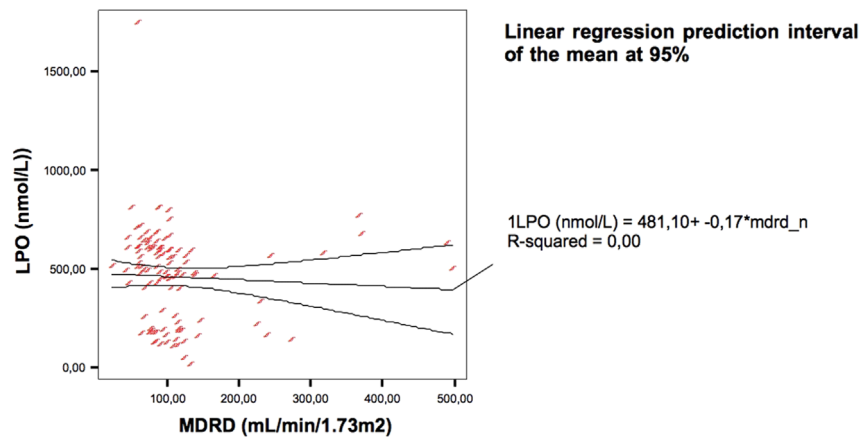


Fig. 2. Correlation between LPO concentration in blood and GFR in patients with OJ.

**Table 3**  
Demographic characteristics and biochemical parameters of the cohorts distributed according to benign and malignant origin.

	Control (n=34)	Benign etiology (n=33)	Malignant etiology (n=72)	p*
<b>Gender (% men)</b>	70%	61%	71%	0.533
<b>Age</b>	57 ± 16.5	66 ± 18.0	70 ± 9.4	0.013 <sup>a</sup> 0.001 <sup>b</sup> 0.818 <sup>c</sup>
<b>Weight (Kg)</b>	73 ± 13.9	74 ± 18.3	73 ± 17.2	0.906
<b>Height</b>	162 ± 9.4	163 ± 9.3	160 ± 17.4	0.978
<b>Systolic blood pressure (mmHg)</b>	122 ± 12.8	121 ± 22.2	123 ± 20.1	0.938
<b>Diastolic blood pressure (mmHg)</b>	73 ± 10.6	68 ± 12.9	70 ± 11.6	0.435
<b>Temperature (°C)</b>	37 ± 0.5	36 ± 0.4	36 ± 0.4	0.889
<b>Jaundice duration (days)</b>	0	9.1 ± 5.20	18 ± 8.6	0.001 <sup>c</sup>
<b>Total Bilirubin (mg/dl)</b>	0.500 ± 0.2000	11.7 ± 7.40	20.2 ± 11.50	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.001 <sup>c</sup>
<b>Direct Bilirubin (mg/dl)</b>	0.230 ± 0.2100	9.0 ± 6.00	16.2 ± 9.60	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.001 <sup>c</sup>
<b>AP(U/L)</b>	66 ± 27.1	528 ± 577.3	757 ± 554.3	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.005 <sup>c</sup>
<b>GGT (U/L)</b>	68 ± 106.6	638 ± 548.2	683 ± 535.7	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.791 <sup>c</sup>
<b>LPO (nmol/L)</b>	163 ± 82.8	473 ± 144.8	603 ± 202	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.001 <sup>c</sup>
<b>GSH (nmol/L)</b>	1.8 ± 1.00	9.5 ± 4.80	11.2 ± 5.40	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.226 <sup>c</sup>
<b>GSH-Px (U/L)</b>	22.8 ± 8.50	15.0 ± 4.20	15.1 ± 14.00	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.170 <sup>c</sup>
<b>SOD (U/L)</b>	15.1 ± 11.10	52 ± 52.6	220 ± 287.8	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.281 <sup>c</sup>
<b>CAT (U/L)</b>	3.8 ± 4.10	4.5 ± 3.30	5.0 ± 5.50	0.250 <sup>a</sup> 0.127 <sup>b</sup> 0.974 <sup>c</sup>

<sup>a</sup> Comparison between control and benign cohorts.

<sup>b</sup> Comparison between control and malignant cohorts.

<sup>c</sup> Comparison between benign and malignant cohorts.

the etiology. The control group was significantly younger than the patient cohort. As glomerular filtration rate decreases with aging, the authors can not exclude a selection bias. This will be discussed later. The oxidative stress markers showed a more intense lipid peroxidation in plasma from patients with OJ and renal dysfunction (Table 2). The alteration of GFR (GFR < 70 ml/min) was related to an increase of peripheral LPO and GSH, and a reduction of SOD (Table 2).

Another key aspect of the study was the correlation between oxidative stress markers and disease progression. Levels of total bilirubin, direct bilirubin, AP and GGT were progressively increased from benign to malignant evolution probably as a consequence of the longer evolution of the disease (Table 3). In this situation, the levels of LPO were much higher in blood from patients with OJ than in controls, reaching the highest levels in those with malignant origin ( $p=0.0001$ ).

A strong positive correlation was observed between the levels of lipoperoxides and bilirubin in blood (Fig. 1) which was in concordance with previous reports showing the pro-oxidant capacity of toxic bile acids [31]. The increased levels of LPO were associated with a rise of GSH and SOD and reduction of GSH-Px in blood from jaundiced patients with benign etiology ( $p=0.0001$ ). Although the tendency of blood levels of antioxidants (GSH and SOD) was to increase in both groups of patients (benign and malignant), the difference between OJ etiologies did not reach statistical significance (Table 3). The explanation may be related to the accumulative alteration of GSH, GSH-Px and SOD (expression or activity) in the different compartment of the body (liver and extrahepatic tissue, and blood cells) by the sustained oxidative stress in patients with OJ of malignant origin. In fact, the progression of experimental jaundice (14 and 21 days) paralleled the increase of LPO and hemolysis, and reduction of total GSH content in blood from obstructed rats [32]. In this study, the level of GSH-Px in liver was reduced throughout all the study [32].

Several experimental studies [32] have demonstrated a reduction of plasma and hepatic levels of GSH in OJ, which tend to recover after therapeutic intervention. The plasma levels of GSH were around 10 times higher in patients with OJ compared to those observed in control subjects (Table 3). The interpretation of this phenomenon may lie to the strong response of the body to adapt to the conditions of oxidative stress increasing the synthesis of GSH during cholestasis. As far as we know, our study is the first reporting GSH content in blood from patients with OJ. Data will be useful to clarify the behavior of this antioxidant in regard to its modulation in liver or intestine.

The multiple linear regression model showed that the benign or malignant etiology, AP, LPO and GSH-Px were related to renal function in patients with OJ. This study demonstrated for the first

time in humans the relationship between the increase of oxidative stress markers during OJ and the associated renal failure. Renal function was affected by the intensity of the biliary obstruction, and the balance between LPO and antioxidant defenses. The fact that age was not identified as affecting the glomerular filtration rate estimation counteracts the previously exposed idea of a possible selection bias.

The logistic regression analysis showed that the age of the subjects and the levels of LPO in blood were predictors of renal dysfunction in OJ patients. At this point we must consider that glomerular filtration rate decline with aging could express a sign of normal senescence instead of a disease. Future researches should consider different cut-off points for renal dysfunction by stratifying by age groups.

Regarding redox imbalance, multivariate analysis overall confirmed the relationship between the oxidative markers in blood and the intensity of OJ and renal dysfunction.

In conclusion, our study is the first report showing in a large series of patients that in situations of OJ, the reduction of GFR or renal dysfunction is related to lipid peroxidation and alteration of antioxidant status in blood. The progression of the disease characteristic of malignant etiology was associated with an exacerbation of lipid peroxidation.

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