Molecular Science

AIMS Molecular Science, 7(4): 374–382.
DOI: 10.3934/molsci.2020018
Received: 26 September 2020
Accepted: 26 November 2020
Published: 30 November 2020

http://www.aimspress.com/journal/Molecular

Research article

Lipid peroxidation, antioxidant defense parameters, and dynamics of surgical treatment in men with mechanical jaundice of various origins

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Abstract: Mechanical jaundice is a severe pathological condition caused by obstruction of the bile duct, usually requiring surgical intervention. Mechanical jaundice occurs in 45–50% of all cases of jaundice of all types, and may be of either non-tumor or tumor origin. Due to involvement of oxidative stress reactions in mechanical jaundice pathogenesis, it is relevant to study the parameters of this process. This study assesses lipid peroxidation-antioxidant defense components in men with mechanical jaundice of non-tumor and tumor origin in the context of surgical treatment. This study examined 47 men with mechanical jaundice of non-tumor origin (MJNT) and 45 men with mechanical jaundice of tumor origin (MJT) (stages I-II of the tumor process). Data from 100 healthy men served as the control. High activity of lipid peroxidation accompanied by falling concentrations of antioxidant enzymes were observed in men with MJNT. Increased primary and final lipid peroxidation products and decreases in almost all studied components of the antioxidant defense system (superoxide dismutase, glutathioneS-transferase, glutathione peroxidase, and ceruloplasmin) were observed. Similar observations emerged for patients with MJT, but with greater changes in parameters. The only indicator of difference between the groups was ceruloplasmin, with lower values in the MJT group. The MJNT group showed decreased thiobarbituric acid reactant values, catalase and ceruloplasmin both values were increased post-surgery. The post-surgery MJT group showed decreased conjugated dienes values and increased catalase and ceruloplasmin values. Thus, in MJNT patients, changes in the lipid peroxidation system relate to the stage of final products, which may serve as a favorable sign, in contrast to the MJT group, where changes concern only the

stage of primary products. Based on the data obtained, antioxidant drugs are advised for patients with mechanical jaundice, with special attention given to the tumor origin of the disease.

Keywords: mechanical jaundice; non-tumor and tumor origin; lipid peroxidation; antioxidants

Abbreviations: AOD: antioxidant defense; CDs: conjugated dienes; CP: ceruloplasmin; GPO: glutathione peroxidase; GST: glutathione-S-transferase; LPO: lipid peroxidation; MJ: mechanical jaundice; MJNT: mechanical jaundice of non-tumor origin; MJT: mechanical jaundice of tumor origin; SOD: superoxide dismutase; TBARs: thiobarbituric acid reactants

1. Introduction

The relevance of studying diseases of the hepatopancreatoduodenal region is currently quite high due to the widespread prevalence and increasing number of patients [1]. Mechanical jaundice (MJ) is the most common among these diseases and is found in 12–45% of cases, mostly men [2]. MJ, or bile duct blockage code K83.1 (ICD 10), is a complex of clinical and morphological manifestations that develop when the bile pathway is disturbed and bile flow from the liver to the duodenum through the main bile ducts is stopped [3]. MJ may be of benign or malignant etiology [1]. The causes of benign processes are diverse and include cholelithiasis, pancreatitis, stenosis of the large duodenal nipple, cicatricial narrowing of the extrahepatic bile ducts, congenital anomalies of the main bile ducts, and parasitic liver diseases [4]. Malignant neoplasms of the pancreas, large duodenal papilla, bile ducts, and liver cancer (primary and metastatic) account for about 20% of MJ causes [5]. Complications of MJ include biliary tract lesions and liver dysfunction, along with systemic complications, including multiple organ failure syndrome [6].

The main pathogenetic mechanisms of development of complications in MJ are: cholestasis with subsequent development of hepatic-cellular insufficiency; disruption of detoxifying mechanisms; immune system imbalance, and oxidative stress reactions [3,7,8]. Despite advances in preoperative assessment and postoperative care, intervention, especially surgical intervention, and MJ management remain associated with high rates of morbidity and mortality, mainly due to sepsis and liver dysfunction [9]. The main trigger mechanism for hepatocyte damage and development of liver failure is hypoxia of liver cells due to increased intra-flow pressure, as well as impaired perfusion of liver tissues [10]. Development of circulatory hypoxia can lead to an intensification of oxidative stress reactions and a lack of antioxidant factors [8]. It has been shown experimentally that violation of the intestinal barrier in MJ is associated with a high frequency of oxidative stress reactions in the intestine [11,12]. Altered expression of intestinal tight junctions and increased cell apoptosis are accompanied by significant changes in the oxidative state of the intestine, an additional important factor contributing to intestinal wall damage in MJ [13,14]. Due to active involvement of oxidative stress reactions in MJ genesis, it is relevant to study the parameters of this process in patients with MJ before and after surgical intervention to develop possible recommendations regarding such intervention.

In this regard, this study assesses lipid peroxidation-antioxidant defense components in men with MJ of non-tumor and tumor origin in the context of surgical treatment.

2. Materials and methods

2.1. Study design

This study is designed as a prospective cross-sectional observational study. We use data from 47 men (average age 52.02 ± 5.18 years) with mechanical jaundice of non-tumor origin (MJNT) and 45 men with mechanical jaundice of tumor origin (MJT) (stages I-II of the tumor process) (average age 53.02 ± 4.8 years). The control group consisted of healthy men (n = 100, average age 48.7 ± 3.9 years). The studied clinical groups were comparable in age, body mass index, alcohol consumption, tobacco smoking, physical activity, and drug use ($p > 0.05$). Criteria for inclusion in an MJ group were: confirmed diagnosis of MJ of non-tumor origin due to gallstone disease or syndrome or MJ of tumor origin, the cause of which was cholangiocarcinoma (stage I–II of neoplasia); total bilirubin levels higher than 3 mg/dL or conjugated bilirubin higher than 2 mg/dL; and ultrasound evidence of extrahepatic bile duct dilatation higher than 12 mm and intrahepatic bile duct dilation 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, and treatment with diuretics and antihypertensives. Informed consent was obtained from all participants. All patients underwent transcutaneous decompression of the bile ducts to stop jaundice. This study was approved by the ethics committee of the Research Institute of Medical Problems of the North, Krasnoyarsk Science Center Siberian Branch of the Russian Academy of Sciences (Protocol No. 7 of 16.11.2012). When examining patients, ethical principles were observed (according to the Helsinki Declaration of the World Medical Association, 1964, ed. 2013).

2.2. Biochemical measurements

Patient and control group peripheral blood biochemical and oxidative stress parameters were measured on admission to hospital and 7 days after surgical intervention.

Blood plasma was obtained after blood centrifugation at 3000 g for 5 min at 4 ℃. Samples were stored at 80 ℃ temperature until laboratory analysis. Dynamic monitoring of patients was carried out throughout the period of hospital admission.

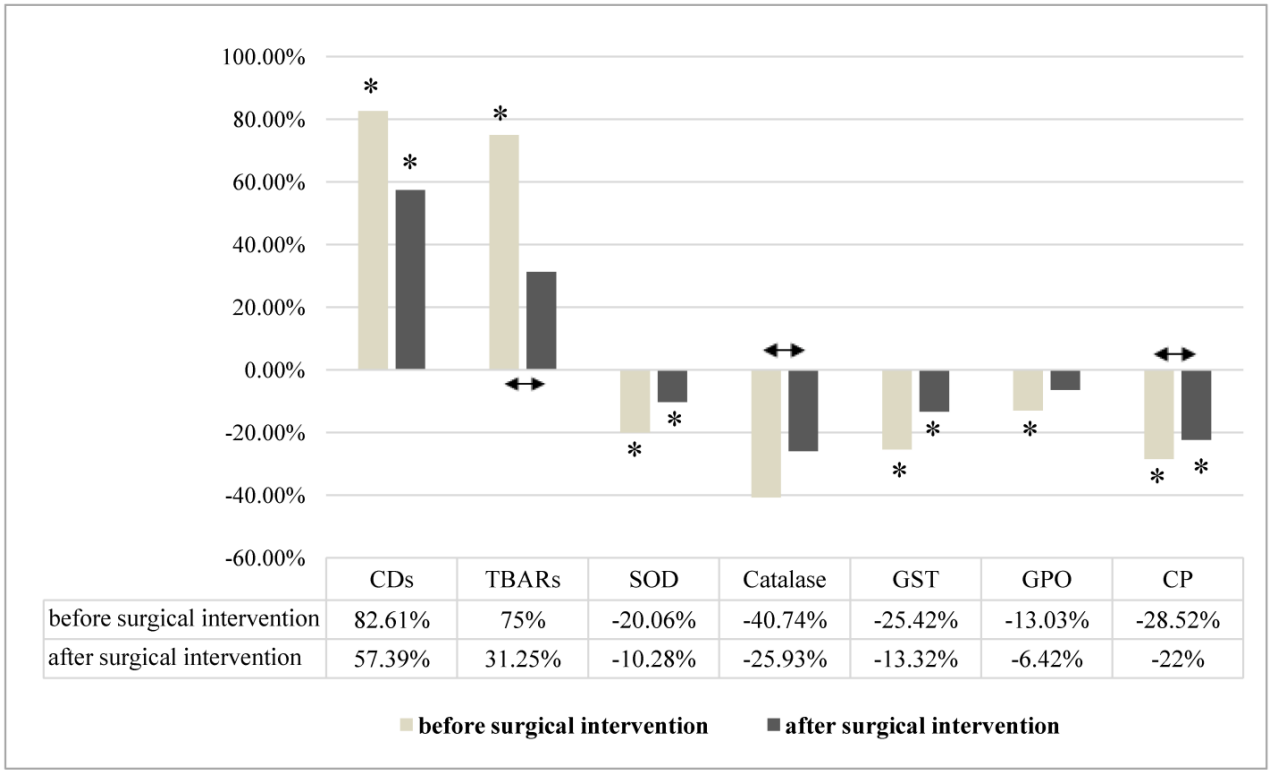
To assess lipid peroxidation-antioxidant defense content (LPO-AOD) system state, the following component content was determined: conjugated dienes (CDs) [15], thiobarbituric acid reactants (TBARs) [16], levels of glutathione-S-transferase (GST) and glutathione peroxidase (GPO) [17], superoxide dismutase (SOD) [18], catalase [17], and ceruloplasmin (CP) [19]. Values were measured using a Shimadzu RF-1501 spectrofluorophotometer (Shimadzu, Japan).

2.3. Statistical procedure

The Statistica for Windows 8.0 application package (Stat Soft Inc., USA, 2008) was used for statistical processing of research results. Determination of proximity of a sample to the normal distribution was performed using the visual-graphical method, the Kolmogorov-Smirnov agreement criteria, and the Lilliefors and Shapiro-Wilk tests. Analysis of statistical significance of the revealed differences in quantitative data was carried out via Mann–Whitney rank criterion. The critical significance level for testing statistical hypotheses was assumed to be $p < 0.05$.

3. Results

LPO-AOD system analysis indicated that there was a statistically significant increase in the content of primary LPO products (CDs 1.83 times higher; $p = 0.001$) and final LPO products (TBARs 1.83 times higher; $p < 0.001$) in the group of patients with MJNT relative to the control group (Figure 1). At the same time, in this group, there was a significant decrease in the levels of almost all AOD system studied components: SOD (1.25 times lower; $p = 0.04$), GST (1.25 times lower; $p = 0.03$), GPO (1.15 times lower; $p < 0.001$) and CP (1.4 times lower; $p = 0.01$) relative to the control group. A similar trend was observed in patients with MJT, but in this group, there were more intense changes in parameters (Figure 2). There was an increase in CDs (2.87 times higher; $p < 0.001$) and TBARs (1.88 times higher; $p < 0.001$), a decrease in SOD (1.38 times lower; $p < 0.001$), GST (2.22 times lower; $p < 0.001$), GPO (1.2 times lower; $p < 0.001$) and CP (1.79 times lower; $p < 0.001$) compared to reference values. Differences between groups were observed only in relation to one indicator, CP, the values of which were lower in the group with MJT (1.4 times lower; $p < 0.001$) (Figure 2).



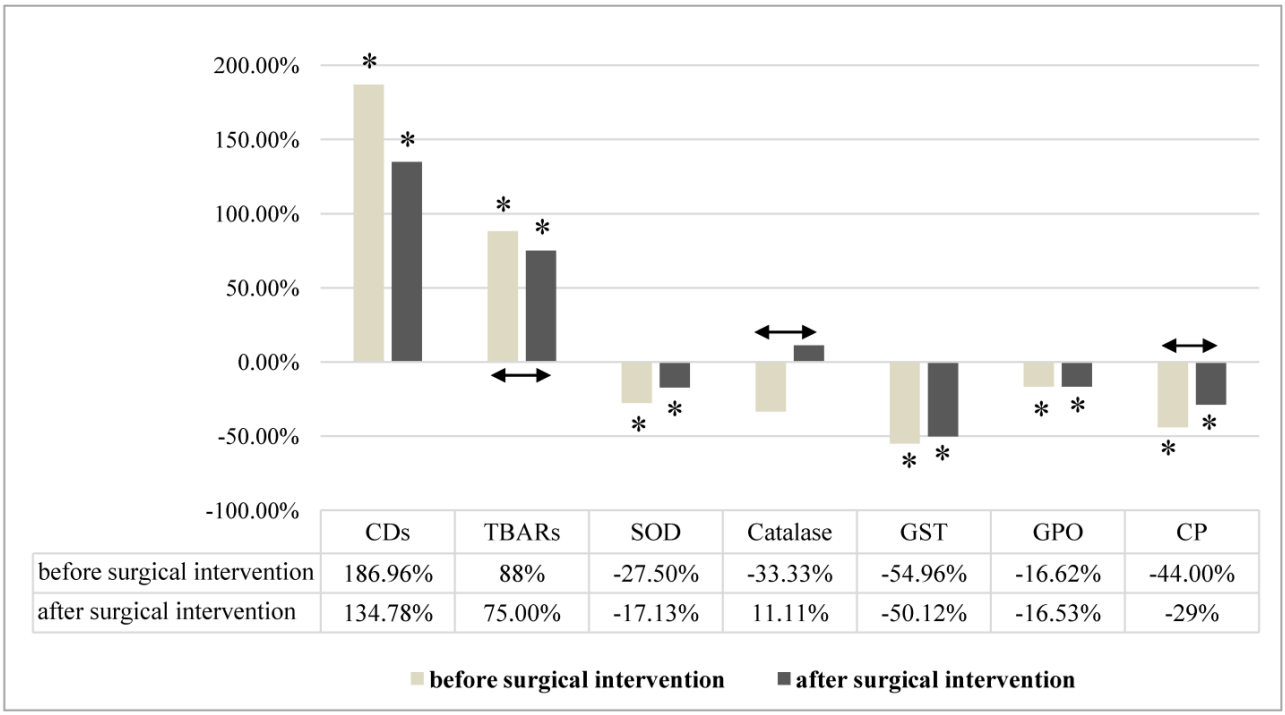
	CDs	TBARs	SOD	Catalase	GST	GPO	CP
before surgical intervention	82.61%	75%	-20.06%	-40.74%	-25.42%	-13.03%	-28.52%
after surgical intervention	57.39%	31.25%	-10.28%	-25.93%	-13.32%	-6.42%	-22%

Figure 1. Changes in parameters of LPO-AOD system in men with MJNT before and after surgical intervention; * indicates statistically significant differences compared to control group; ↔ indicates statistically significant differences in men with MJNT after surgical intervention compared to group before surgical intervention.

After surgical intervention, average CDs values in patients with MJNT compared to control group values remained elevated (1.57 times higher; $p < 0.001$), while values of some components of the AOD system decreased slightly: SOD (1.1 times lower; $p = 0.03$), GST (1.15 times lower; $p = 0.04$) and CP

(1.29 times lower; $p = 0.043$) (Figure 1). In the MJNT group post-surgery, relative to pre-surgery data, there was a decrease in TBARs values (1.33 times lower; $p = 0.003$), an increase in catalase values (1.25 times higher; $p = 0.028$), and an increase in CP values (1.09 times higher; $p = 0.03$) (Figure 1).

A similar trend was observed in the MJT group: an increase in the content of CDs (2.35 times higher; $p < 0.001$) and TBARs (1.75 times higher; $p < 0.001$), a decrease in SOD (1.21 times lower; $p < 0.001$), GST (2 times lower; $p = 0.002$), GPO (1.2 times lower; $p = 0.001$) and CP (1.4 times lower; $p = 0.003$) relative to the control group (Figure 2). In the MJT group post-surgery, relative to pre-surgery data, there was a decrease in CDs values (1.22 times lower; $p = 0.037$), an increase in catalase values (1.67 times higher; $p = 0.0009$), and an increase in CP values (1.27 times higher; $p = 0.03$) (Figure 2).



	CDs	TBARs	SOD	Catalase	GST	GPO	CP
before surgical intervention	186.96%	88%	-27.50%	-33.33%	-54.96%	-16.62%	-44.00%
after surgical intervention	134.78%	75.00%	-17.13%	11.11%	-50.12%	-16.53%	-29%

Figure 2. Changes in parameters of LPO-AOD system in men with MJT before and after surgical intervention; * indicates statistically significant differences compared to control group; ↔ indicates statistically significant differences in men with MJT after surgical intervention compared to group before surgical intervention.

4. Discussion

This study found that MJNT leads to significant activation of lipid peroxidation processes: increases in both primary (CDs) and final (TBARs) LPO products, at levels more pronounced ~~than~~ in the MJT group. LPO products are classified as toxic compounds that have a damaging effect on various components of the cell, so their increase can have an extremely negative impact on the state of the body as a whole [20–22]. Development of oxidative stress in MJ can be initiated by the absence of normal bile flow, which deprives the intestine of its bacteriostatic, neutralizing, and

trophic properties [23]. There is an increase in bacterial load and mucosal atrophy, which contributes to translocation of bacteria and endotoxins into the portal circulation [24]. Cholestasis reduces Kupffer-cell clearance ability, which provokes ingress of bacteria and endotoxins further into the systemic bloodstream. A systemic inflammatory reaction develops, which exacerbates intestinal barrier dysfunction and cholestatic liver damage [25,26]. In complex endotoxemia, high levels of cytokines and bile acids are important stimulators of oxidative damage in various organs, including the intestines. Studies on experimental animals have shown a significant increase in LPO products in the intestinal mucosa, as well as a general imbalance between protein or non-protein thiols [10,14]. Data on increased intestinal oxidative stress in MJ have also been confirmed in clinical settings [3]. It is known that depending on the duration of the pathological process, oxidative stress can cause both cell death and activation of adaptive defense mechanisms that lead to the new ratio of reactive oxygen species/antioxidants [27].

This study found a significant decrease in almost all the studied components of the AOD system, SOD, GST, GPO, and CP, in the MJNT group. A similar situation, but with more pronounced changes, was observed in the MJT group. It is believed that even small fluctuations in SOD levels indicate a shift in metabolism toward the predominance of pro-oxidant processes [28]. Glutathione system imbalance may also indicate activation of LPO reactions [29]. CP, characterized as a protein involved in metabolism of free radicals in extracellular compartments, is a copper-binding glycoprotein. The antioxidant function of CP may also be related to its ability to bind copper ions, which are well-known pro-oxidant catalysts [30]. Thus, severe insufficiency of these components may negatively affect antioxidant status in patients with MJ.

Under conditions of bile duct decompression in MJ, increased oxygenation of liver tissues occurs, which contributes to the phenomenon of “oxygen paradox”, when the supply of the usual amount of oxygen to ischemic tissues, where pro-oxidants predominate over antioxidants, leads to additional formation of reactive oxygen species [8]. These conditions lead to further cell membrane lipid layer damage and changes to physical and chemical properties, followed by inflammation activation at both local and systemic levels [31]. Potential mechanisms of activation of oxidative stress in the intestinal region in MJ include: increased levels of bile acids, systemic endotoxemia, inducible nitric oxide synthase increased expression [3,32], increased neutrophil chemotaxis and generation of superoxide anions [33], and antioxidant component systemic level decreases [8].

Surgical intervention improved LPO-AOD scores in the MJNT group in comparison with both the control group and with preoperative data. Thus, after surgical intervention, patients with MJNT showed a decrease in TBARs and an increase in catalase and CP levels. In the post-surgery MJT group, the parameters of the LPO-AOD system also changed in comparison with the control group and with pre-surgery data. In this group, there was a decrease in the primary products of LPO and CDs, and an increase in the level of catalase and CP relative to pre-surgery data. Note that surgery can provoke development of septic complications post-surgery [3,26,34]. In addition, in the postoperative period, progression of liver failure and endogenous intoxication is noted; this is the main cause of death in MJ [1,4]. Patients with MJ in the postoperative period show decreased humoral immunity parameters, development of leukocytosis, and decreased phagocytic activity [26]. There is disturbance of the functional activity of macrophages and granulocytes, and expression of HLA-DR antigens decreases rapidly on blood monocytes after surgery [35]. All classes immunoglobulins, especially IgG, increase, along with the number of T-suppressors, suppressor macrophages, synthesis of interleukins-4,-10, transforming growth factor, and prostaglandin E;

in addition, the function of natural killer cells is inhibited and the number of T helper cells decreases [35,36]. Due to the numerous disorders of the immune response in MJ, detoxification of the body plays an important role in ensuring a favorable postoperative outcome. One detoxification measure is inactivation of toxic products of free radical reactions, since they play a decisive role in the functioning of the immune system [37]. It is known that the damaging effect of free radicals is realized both as a result of their direct effect on proteins, enzymes, and nucleic acids, and through LPO products (lipid hydroperoxides, conjugated dienes, aldehydes, formed at different stages of the chain reaction [38]. The most toxic final products are TBARs, which can inhibit DNA synthesis, induce apoptosis and thereby suppress the proliferation, maturation, and growth of body cells; TBARs also have a strong carcinogenic effect and cause mutational changes [39]. An increase in toxic products of LPO, as a rule, indicates rapid involvement of LPO processes in the pathogenetic mechanisms of structural and functional disorders in the cells of organs and tissues. Thus, a decrease in the concentration of TBARs products in patients with MJNT may serve as a favorable sign in the postoperative period, unlike the MJT group, where this change is not observed.

5. Conclusion

This study shows high activity of lipid peroxidation processes accompanied by decreased antioxidant enzyme concentration in men with MJ, regardless of disease origin. At the same time, the presence of malignant growth in patients with MJ is characterized by more pronounced changes in lipid peroxidation-antioxidant defense system. Post-surgery, patients with MJNT experienced a decrease in final products; in patients with MJT, the level of primary products decreased, while catalase and CP increased in both groups relative to pre-surgery data. Based on the data obtained, it is advisable to include antioxidant drugs in treatment of patients with MJ, with special attention given to the tumor origin of the disease.

Conflict of interest

All authors declare no conflict of interest regard to this paper.

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