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The Induction of Antioxidant Catalase Enzyme With Decrease of Plasma Malonidialdehyde: An Important Reactive Oxidative Species Inhibiting Mechanism

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Abstract. *Background/Aim: The simultaneous increase of antioxidant CAT (catalase) enzyme and plasma MDA (malonidialdehyde) concentrations versus the numeric rating scale (NRS) pain score following surgery is unknown. Patients and Methods: The study included 114 patients with gallstone disease and 29 patients in the cancer group. Results: Following surgery, the plasma CAT concentrations increased and plasma MDA concentrations decreased in all patients and especially in cancer patients. The linear mixed model time-effect was statistically significant in CAT and MDA ($p<0.001$ and $p=0.02$, respectively). In addition, a significant correlation between NRS pain score values and plasma MDA median concentrations in cancer patients was identified ($r=0.430$, $p<0.001$). Conclusion: The plasma MDA concentrations decreased and CAT concentrations increased significantly in all patients and especially in cancer patients following surgery. The simultaneous increase of antioxidant CAT enzyme with the decrease of plasma MDA may be an important ROS inhibiting mechanism to help patients return to normal antioxidant-oxidant status.*

Lipid peroxidation is a process where reactive oxygen species (ROS) attack lipids containing carbon double bonds (C-C), especially in polyunsaturated fatty acids (PUFAs). Lipid peroxidation of unsaturated lipids produces a variety of ROS products and has an important role in cell biology and human health. The main products of lipid peroxidation are lipid hydroperoxides (LOOH) while the secondary products consist of different aldehydes, of which the most harmful product is malonidialdehyde (MDA) (1-3). MDA is a toxic substance reacting with deoxyadenosine in DNA and forming DNA adducts, which are mutagenic and carcinogenic (1-3). The harmful effects of MDA could be neutralized by substances known as antioxidants such as vitamin C and vitamin E, which may inhibit lipid peroxidation. Catalase (CAT) is one antioxidative substance, which plasma concentrations have shown to have inverse correlation to analgesic doses during the first 24 hours following surgery (4) and an inverse correlation to numeric rating scale (NRS) pain scores following surgery in midline laparotomy patients (5). Our previous article showed that the cancer patients with midline laparotomy had significantly lower plasma MDA concentrations postoperatively, whereas the postoperative alteration of median plasma CAT levels in cancer patients were significantly higher in the benign group of patients (6). Therefore, we felt it appropriate to carry out a study to compare the lipid peroxidation biomarker MDA levels to antioxidative biomarker CAT levels and NRS pain scores.

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Key Words: Gallstone disease, cancer, surgery, plasma MDA, plasma CAT, NRS pain score.

Patients and Methods

The study was approved by the Ethics Committee of Kuopio University Hospital District, Kuopio, Finland (DNRO 27/02/2013), it was registered in the ClinicalTrials.gov database (ClinicalTrials.gov Identifier: NCT01723540, Consort diagram, Figure 1), and was conducted in accordance with the Declaration of Helsinki. The study included 114 patients with cholelithiasis in the Laparoscopy Cholecystectomy (LC) (n=54) or Minilaparotomy Cholecystectomy (MC) (n=60) groups (Figure 1) and the cancer group, recruited from our previous study, which included 10 patients with gastrointestinal cancer and 19 patients with gynecological cancer (7-9). The surgical

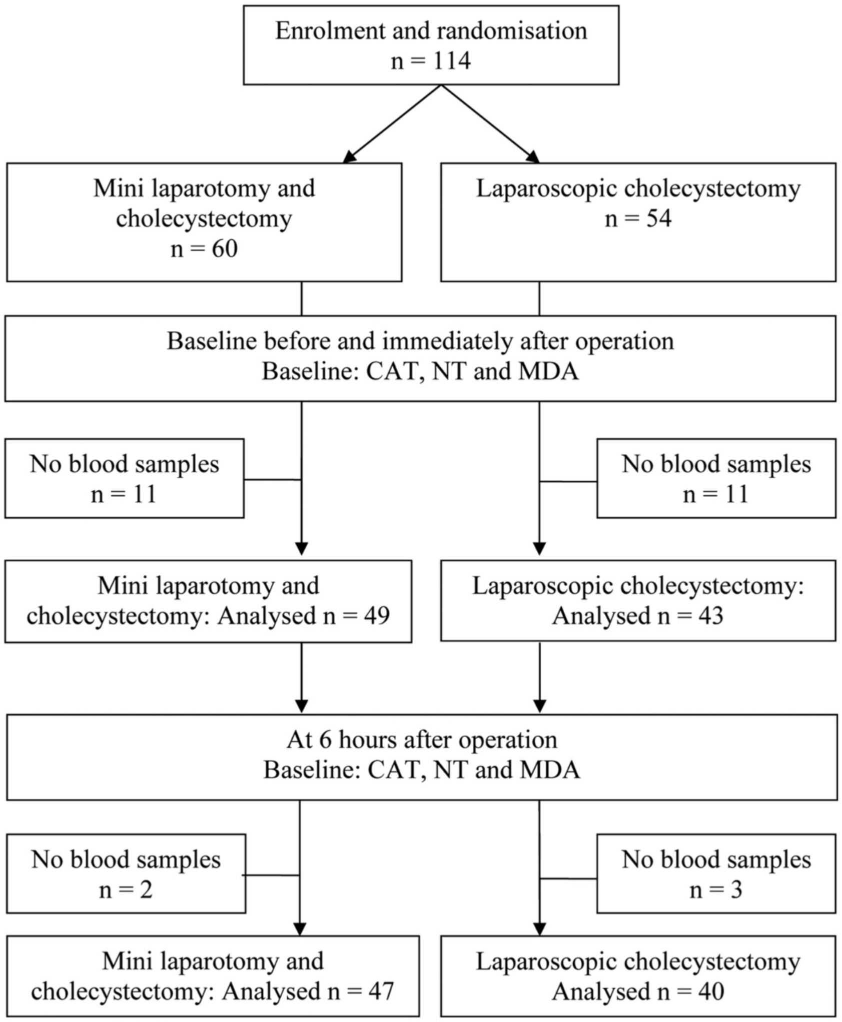

Figure 1. *Study flow chart.*

techniques used were standardized for both groups. The overall pain was measured using an 11-point numeric rating scale (NRS; 0=no pain; 10=most pain). The study protocol was fully described in our earlier original work (10-12).

EDTA-blood samples were taken before surgery (PRE), immediately after surgery (POP1) and 6 h post-operatively (POP2) and centrifuged at 1,000G (2,900 rpm) for 15 min. The study protocol of CAT and NT were fully described in our earlier original works (4, 5, 13, 14). Plasma MDA concentrations were determined by using MDA (Malondialdehyde) ELISA Kit (E-EL-0060, Elabscience, Biotechnology Inc. Houston, Texas, USA). The manufacturer's intra-assay and the inter-assay coefficients of variation (CVs) were 5.6% and 6.28%, respectively.

Data are presented as means and standard deviations or frequencies and percentages, where appropriate. Differences in baseline characteristics between groups were tested by the Fisher's exact test and in the case of continuous data, the analysis was performed by *t*-test. Group differences at three time points were tested by the Wilcoxon signed rank test and the Kruskall-Wallis-test.

Table I. *Clinical data of the study groups. Data are mean (standard deviation) or number of cases.*

Variable	Mini laparotomy n=60	Laparoscopy n=54	*p*-Value
Age, years	50.7 (13.2)	53.2 (13.1)	0.316
Gender male/female	11/49	18/36	0.066
Height, cm	167.4 (7.6)	168.9 (9.9)	0.355
Weight, kg	77.3 (14.4)	83.0 (17.4)	0.057
BMI, kg/m^2	27.6 (4.4)	29.1 (5.6)	0.111
Operative time, min	70.0 (26.9)	70.1 (35.3)	0.976
Time in the operative room, min	120.4 (28.5)	127.1 (35.8)	0.287
Perioperative bleed, ml	41 (59)	31 (39)	0.290
Conversion rate, n	3	3	1.000*
Length of the skin incision(s), mm	49.7 (12.1)	78.3 (22.7)	<0.001

BMI: Body mass index. *T*-test and *Fisher's exact test were used.

Table II. *Plasma catalase (CAT), nitrotyrosine (NT) and malonidialdehyde (MDA) concentrations in minicholecystectomy (MC) and laparoscopic cholecystectomy (LC) patients versus cancer patients. Plasma concentrations were measured before (PRE), immediately after (POP1) and 6 h after (POP2) surgery. Median (interquartile range) concentrations are shown. Kruskall-Wallis test and linear mixed model was used.*

Marker	MC	LC	Cancer	*p*-Value
CAT (pg/ml)				**<0.001**
PRE	0.75 (0.42-1.36)	1.09 (0.56-1.60)	0.73 (0.48-1.30)	0.384
POP1	0.79 (0.48-1.37)	0.93 (0.56-1.65)	1.46 (1.13-2.36)	0.001
POP2	0.76 (0.43-1.22)	1.02 (0.67-1.58)	1.12 (0.68-1.50)	0.069
NT (pg/ml)				**0.054**
PRE	3.79 (2.88-5.16)	4.39 (2.48-5.71)	5.67 (4.10-8.10)	0.001
POP1	4.11 (2.96-5.26)	4.40 (2.76-5.76)	5.28 (3.41-6.44)	0.078
POP2	4.25 (3.00-5.45)	4.51 (2.96-5.84)	4.69 (4.09-6.27)	0.243
MDA (ng/ml)				**<0.001**
PRE	877 (646-1002)	787 (634-1133)	868 (571-1037)	0.811
POP1	844 (635-1093)	890 (694-1186)	589 (392-730)	<0.001
POP2	864 (682-1065)	905 (606-1156)	560 (411-758)	<0.001

Linear mixed effect model *p*-Values for interaction time group are in bold. Time-effect in linear mixed model in plasma catalase, nitrotyrosine and malonidialdehyde in cancer group was statistically significant ($p<0.001$, $p=0.009$ and $p<0.001$, respectively).

The plasma CAT, NT and MDA concentrations and differences in the patients with MC, LC and cancer were tested by the Mann-Whitney *U*-test. The linear mixed effect (LME) model was used to test the interaction group time effect. In LME analysis plasma concentrations were log transformed. The results of the laboratory measurements are presented as median concentrations with interquartile range as distributions were skewed to the right. The Pearson's method was used to test for correlation for plasma NT concentrations *versus* MDA concentrations. Data were analyzed by IBM SPSS statistical software (IBM Corp. released 2013, IBM SPSS Statistics for Windows, version 22.0, IBM Corporation, Armonk, NY, USA). *p*-Values under 0.05 were considered statistically significant.

Results

In cholecystectomy patients, randomized either in the MC or LC groups, there were no significant difference in mean age, height, weight, mean body mass index (BMI), operative time, time in the operative room, perioperative bleed or conversion rate. The skin incision was significantly longer in the LC than in the MC group ($p<0.001$, Table I).

The median plasma oxidative stress concentrations of the NT and MDA biomarkers between the MC and LC groups were quite similar (Table II). Changes in plasma MDA and NT concentrations following surgery are shown in Table II. Lipid peroxidation biomarker MDA increased significantly following surgery in LC patients and decreased significantly in cancer patients (Table II). The statistically significant linear mixed model (LME) *p*-Values for interaction time in MC patients, LC patients and cancer patients are shown in Table II ($p<0.001$, $p=0.05$ and $p<0.001$, respectively). In cancer patients, the LME time-effect was statistically significant in CAT, NT and MDA concentrations ($p<0.001$, $p=0.009$ and $p<0.001$, respectively). The antioxidant plasma CAT concentrations increased and plasma MDA decreased significantly in all patients and especially in cancer patients (Table II). The LME time-effect of the plasma CAT and MDA concentrations preoperatively and following surgery was significant ($p=0.001$ and $p=0.02$, respectively, Table III).

There was a significant correlation in the NRS pain score values *versus* the plasma MDA values in cancer patients ($r=0.430$, $p<0.001$, Figure 2) and a significant correlation in the median MDA *versus* median NT plasma concentrations in all patients was found ($r=0.445$, $p<0.001$, Figure 3).

Table III. *Alteration of plasma catalase (CAT), nitrotyrosine (NT) and malonidialdehyde (MDA) concentrations following surgery. Plasma concentrations were measured before (PRE), immediately after (POP1) and 6 h after operation (POP2). Median (interquartile range) concentrations are shown.*

Marker	All patients	Alteration	*p*-Value
CAT (pg/ml)			**0.001**
PRE	0.79 (0.44-1.50)	PRE *vs*. POP1	0.001
POP1	1.01 (0.56-1.68)	POP1 *vs*. POP2	0.027
POP2	0.92 (0.57-1.48)		
NT (pg/ml)			**0.071**
PRE	4.38 (3.40-5.58)	PRE *vs*. POP1	0.039
POP1	4.16 (3.17-5.37)	POP1 *vs*. POP2	0.077
POP2	4.31 (3.38-5.51)		
MDA (ng/ml)			**0.020**
PRE	880 (649-1128)	PRE *vs*. POP1	0.001
POP1	839 (589-1127)	POP1 *vs*. POP2	0.943
POP2	857 (600-1132)		

The Wilcoxon signed-rank test and linear mixed model was used. Linear mixed model *p*-Values for time effect are in bold.

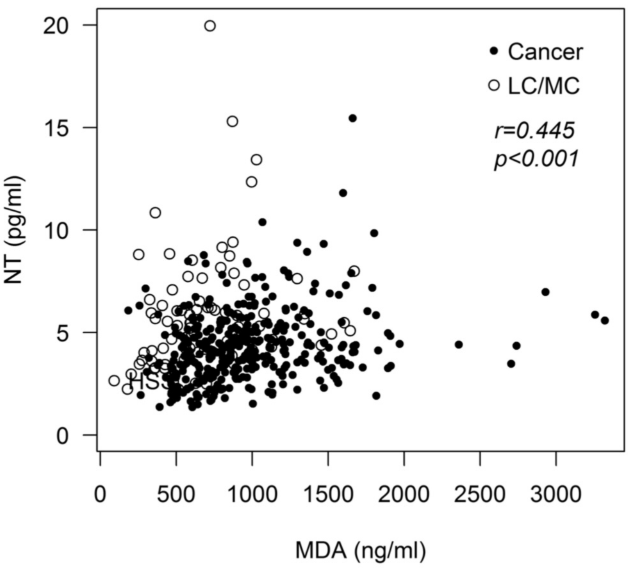

Figure 2. *Scatter plots of the plasma malonidialdehyde (MDA) concentration versus pain assessed using a 11-point numeric rating scale (NRS; 0=no pain; 10=most pain) at 8 hours postoperatively (NRS_8) in cancer patients (r=0.430, p<0.001).*

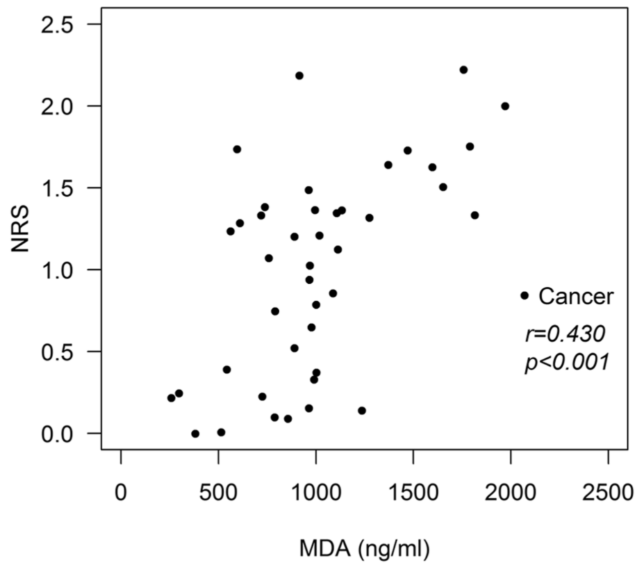

Figure 3. *Jitterplot of plasma malonidialdehyde (MDA) concentration versus plasma nitrotyrosine (NT) concentration in cholecystectomy and cancer patients (r=0.445, p<0.001).*

Discussion

MDA is an end product of lipid peroxidation of PUFAs located in cell membranes forming DNA adducts, which are mutagenic (1-3). Earlier studies of MDA biomarker are showing the connection between oxidative stress and cancer (2, 3), cardiovascular diseases (2, 3), diabetes (2, 3, 16), liver disease (2, 3), Alzheimer's disease (1, 2, 3, 17, 18), Parkinson's disease (1) and major depressive disorders (19). In addition, MDA is used as a biomarker of acetaminophen hepatotoxicity (20) and to identify ROS changes of bladder tissue in the initial phase of diabetes (16). Tsounapi *et al.* (16) showed that MDA levels in the bladder wall were significantly higher in the diabetes group compared to other study groups. They also suggested that antioxidant substances such as taurine and resveratrol could provide cytoprotection of bladder tissue by inhibiting MDA (16).

Lipid peroxidation, ROS and reactive nitrogen species (RNS) results in an imbalance between the formation of ROS species and decreased ability to detoxify and to inhibit the damage. The negative effects of ROS/RNS can be neutralized by substances known as antioxidants. Living cells contain large number of antioxidants, vitamin C and E, carotenoids and flavonoids (21, 22). Interestingly, oligomeric proanthocyanidins (OPCs) extracted from grape seeds have been shown to have higher antioxidant capability than vitamin C or E (21). Lu *et al.* (24) studied the effect of OPCs and showed that OPC supplementation significantly reduced the plasma MDA biomarker concentrations and increased the plasma CAT concentrations, thereby inhibiting the ROS substances and increasing the antioxidant capacity of patients with COPD (Chronic Obstructive Pulmonary Disease).

The most common method used to measure MDA in the earlier studies is the thiobarbituric acid substances (TBARS) assay. The TBARS test is based on the reactivity of thiobarbituric acid toward MDA. This test was first used by food chemists to evaluate degradation of fats and oils (3). Although, TBARS is not specific enough due to interference from substances that are produced during the assay and presence of false chromogens, Spanidis *et al.* (23) showed that TBARS reactive substances detection is a useful biomarker of oxidative stress in obese sepsis patients in the intensive care. Several methods for measuring free and total MDA are available; including gas chromatography mass spectrometry and liquid chromatography-mass spectrometry (8). In addition, the ELISA sandwich assay has also been used to measure plasma MDA concentrations (6).

The median plasma concentrations of NT and MDA between the MC and LC patients were quite similar and it seems that cholecystectomy, in either MC or LC, causes only a moderate oxidative stress response. However, the median plasma MDA concentrations decreased and CAT concentrations increased significantly in all patients and especially in cancer patients following surgery. In addition, the decrease of plasma MDA and increase in plasma CAT concentrations showed statistically significant *p*-Values in the linear mixed model. Accordingly, the simultaneous increase of the antioxidant CAT enzyme with the decrease of lipid peroxidation biomarker MDA may be an important ROS inhibiting mechanism to help patients return normal antioxidant-oxidant status. In addition, our results of a significant correlation between the plasma MDA levels *versus* the NRS pain scores are in line with the results shown in the systematic review of Yiannakopoulou *et al*. (26).

In conclusion, the efficient inhibition of ROS requires coordinate action of several cellular antioxidant enzymes. In this study, the median plasma CAT concentrations in all patients and especially in cancer patients increased significantly following surgery and the antioxidant CAT enzyme could help patients return normal antioxidant-oxidant status *via* enhancing CAT to neutralize ROS substances and to supress oxidative stress.

Conflicts of Interest

The Authors report no conflicts of interest or financial ties to disclose. The Authors alone are responsible for the content and writing of this article.

Authors' Contributions

MR, VK, IS, VK, JK, SA and ME were responsible for the recruitment of study participants and clinical and laboratory investigations and collection of data. TS performed the statistical analyses. All authors contributed to the data analysis, drafting and revising the manuscript, read and approved the final manuscript.

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