

Anti-oxidative/anti-inflammatory paraoxonase activity and lipid alterations after total splenectomy and autologous spleen transplantation in pigs

**Romana Turk^{1*}, Dražen Vnuk², Ante Svetina¹, Zlata Flegar-Meštrić³,
Nika Brkljača Bottegaro², and Dubravka Juretić⁴**

¹*Department of Pathophysiology, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia*

²*Clinic for Surgery, Orthopedics and Ophthalmology, Faculty of Veterinary Medicine,
University of Zagreb, Zagreb, Croatia*

³*Institute of Clinical Chemistry, Clinical Hospital "Merkur", Zagreb, Croatia*

⁴*Department of Medical Biochemistry and Haematology, Faculty of Pharmacy and Biochemistry,
University of Zagreb, Zagreb, Croatia*

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ABSTRACT

The objective of this study was to investigate serum PON1 activity and lipid and lipoprotein status after total splenectomy and autologous spleen transplantation in pigs, in order to assess the effect of surgical stress and trauma on PON1 activity and lipid metabolism. Nineteen piglets used in the experiment were randomly divided into three groups: sham-operation with spleens intact (n = 6), total splenectomy (n = 6), and splenic autotransplantation (n = 7) with small fragments of the spleen autotransplanted into the greater omentum. The blood samples were taken just before surgery and on the 1st, 5th, 12th, 26th and 40th days postoperatively. PON1 activity, total cholesterol and HDL-C were assayed in the sera. PON1 activity was significantly decreased postoperatively in splenectomized pigs (on days 5, 12 and 40) and in autotransplanted pigs (on days 5, 12, 26 and 40) while there were no PON1 changes in the sham-operated. In sham-operated pigs, total cholesterol was significantly decreased only on the 12th day postoperatively, while HDL-C was significantly decreased postoperatively on the 1st, 5th, 12th, 26th and 40th days with the minimum value on the 12th day. In splenectomized pigs total cholesterol was significantly decreased on the 5th, 12th, 26th and 40th days postoperatively, while HDL-C was decreased as well on the 1st, 5th, 12th and 40th days and both were the lowest on the 12th day. In pigs with autologous splenic transplants, total cholesterol was significantly decreased on the 12th, 26th and 40th days, while there was no difference in HDL-C. The results demonstrated decreased PON1 activity and alterations

*Corresponding author:

Romana Turk, PhD, Department of Pathophysiology, Faculty of Veterinary Medicine, University of Zagreb, Heinzelova 55, 10000 Zagreb, Croatia; Phone: +385 1 2390 183; Fax: +385 1 2390 184; E-mail: rturk@vef.hr

in the concentrations of total cholesterol and HDL-C after surgery due to surgical trauma and post-surgical inflammatory response.

Key words: paraoxonase, serum lipids, splenectomy, spleen autotransplantation, surgical trauma, inflammation

Introduction

The spleen is an important lymphatic organ with a major role in many specific and unspecific immune reactions (PEARSON et al., 1978). Until the early 1900s, the spleen was regarded as a nonessential tissue that could be removed without harming the patient. However, splenectomy may be followed by overwhelming postsplenectomy infection and lethal sepsis due to removal of the splenic macrophages and B cells that either phagocytose bacteria and other pathogens or produce specific antibodies (TIEMENS and LEEMANS, 1992; NEWLAND et al., 2005). Thus, experimental animal studies have been done to establish the autologous splenic transplantation as the only possible method for preserving splenic tissue and its immunoprotective effects against infection and inflammation after spleen trauma or due to haematological diseases (MARQUES et al., 2002; BIERTHO et al., 2004; VNUK, 2006).

There is a wide range of metabolic responses that occurs in surgical trauma (KUDOH et al., 2001). Necrotic cells originating from tissue lesion could trigger local and systemic inflammatory cascade with the activation of inflammatory cells and production of cytokines that mediate the acute phase response (APR) following surgical trauma (SIDO et al., 2004). APR comprises early, highly complex reactions of the host including synthesis of acute phase proteins, exceeded production of reactive oxygen metabolites as well as alterations in lipid and lipoprotein metabolism (HEINZELMANN et al., 1997; KHOVIDHUNKIT et al., 2004). In addition, during APR there is a reduction of several plasma proteins that are associated with high density lipoprotein (HDL), such as paraoxonase-1, PON1 (VAN LENTEN et al., 1995; FEINGOLD et al., 1998). HDL is an important segment of APR and its protective role is in part related to the antioxidative enzyme, PON1, associated with it (NAVAB et al., 2001). PON1 (E.C. 3.1.8.1) plays an important physiological role in lipid metabolism through the hydrolysis of oxidized lipids that are pro-inflammatory compounds, providing protection against oxidative stress. Thus, the anti-oxidative property of PON1 is responsible for the anti-oxidative/anti-inflammatory actions of HDL (DURINGTON et al., 2001; AVIRAM and ROSENBLAT, 2004). The significance of PON1 in metabolic diseases associated with oxidative stress and lipid metabolism disorders is well documented in humans (LA DU et al., 1999). In animal research, the series of our studies have shown the involvement of PON1 in oxidative stress and the lipid metabolism in cows (TURK et al., 2004, 2005a, 2005b, 2007).

Up to now, studies on PON1 in pigs have not been documented. The purpose of this study was to investigate serum PON1 activity and lipid and lipoprotein status after total

splenectomy and autologous spleen transplantation in pigs in order to assess the effect of surgical stress and trauma on PON1 activity and lipid metabolism.

Materials and methods

Animals, anaesthesia and surgery. The experimental protocol was approved by the Department of Veterinary Science, Ministry of Agriculture, Republic of Croatia and was conducted in accordance with the guidelines for the treatment of laboratory animals. Emotional reassurance (gentle restraint, petting and talking) was provided by the handler. Nineteen piglets of either sex, aged 3 months, weighing 19-26 kg were used in the experiment. In each animal food was withheld for 12 h and water for 2 h before the experiment.

The animals were premedicated with 2 mg kg⁻¹ i.m. of xylazine, and left auricular vein was catheterized percutaneously for continuous infusion of lactated Ringer's solution at a rate of 10 mL kg⁻¹ h⁻¹ during surgical procedures and for the administration of drugs. Anesthesia was induced with 5 mg kg⁻¹ i.v. of ketamine and 10 µg kg⁻¹ i.v. fentanyl, and the animals were intubated, connected to a circle system and maintained on spontaneous ventilation. Anesthesia was maintained with 1.5% isoflurane and continuous intravenous infusion of fentanyl in a dose of 0.8 µg kg⁻¹ min⁻¹. Supplemental doses of ketamine were given during surgery to maintain sufficient anesthesia depth. Perioperative antibiotic prophylaxis was administered using 20 mg kg⁻¹ ampicillin and sulbactam i.v.

After induction of anesthesia, animals were randomly divided into three groups: sham-operated pigs with spleens intact (control group, n = 6), splenectomized pigs (n = 6), and splenectomized pigs with small fragments of 20% mass of the spleen autotransplanted into the greater omentum (n = 7).

Blood sampling and experimental protocol. Blood samples were taken from the v. jugularis into the Vacutainer® tubes containing clot activator (Becton Dickinson & Company, Plymouth, UK) just before surgery and on the 1st, 5th, 12th, 26th and 40th days postoperatively. After clotting for two hours at room temperature, blood samples were centrifuged at 3000 rpm for 15 min and serum samples were stored at -70 °C until analysis.

PON1 activity assay. The PON1 activity was assayed by the slightly modified method of hydrolysis of paraoxon previously described by MACKNESS et al. (1991) and SCHIAVON et al. (1996). Briefly, the serum sample was added to 0.1 M Tris-HCl buffer, pH 8.0 containing 2.0 mM paraoxon (O,O-diethyl-O-p-nitrophenylphosphate, Sigma Chemical Co, London, UK) as a substrate, 2.0 mM CaCl₂ and 1 mM NaCl. The formation of p-nitrophenol was monitored bichromatically at 410/480 nm at 37 °C on Olympus AU 600. The PON1 activity was expressed in international units (U/L) as the amount of substrate hydrolyzed per minute and per litre of serum (µmolmin⁻¹/L).

Lipid status measurements. Total cholesterol and HDL-cholesterol concentrations were measured by standard commercial kits (Olympus Diagnostica GmbH, Hamburg, Germany). All methods were performed using an automatic analyzer Olympus AU 600 (Olympus Mishima Co., Ltd., Shizuoka, Japan).

Statistical analysis. Normality and equal variance were tested using the Kolmogorov-Smirnov test and Leven's test. In order to assess significant differences between investigated groups, ANOVA was applied using SPSS software (SPSS Inc., Chicago, Illinois, USA). Pearson correlation coefficient was used to examine the correlation between two parameters. Statistical significance was based on values $P < 0.05$.

Quality control of measurements. The quality control for the parameters measured was based on control of accuracy and control of imprecision. Control of accuracy was performed for total cholesterol and HDL-C concentrations using commercial control sera (Roche Diagnostics and Olympus Diagnostica, respectively). The biases for these parameters were 1.6% and 1.0%, respectively. Control of imprecision was performed using pool serum samples for the PON1 activity, total cholesterol and HDL-C concentrations. The intra-assay CVs for these parameters were 0.90%, 0.99% and 0%, respectively, while the inter-assay CVs were 7.2%, 6.3% and 5.9%, respectively.

Results

PON1 activity. PON1 activity in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants is given in Table 1. There were no statistical differences in PON1 activity in sham-operated pigs before surgery and the values after surgery, on the 1st, 5th, 12th and 40th days postoperatively. In splenectomized pigs the PON1 activity was significantly decreased postoperatively on the 5th, 12th, 26th and 40th days compared to the value before surgery ($P < 0.05$) with the lowest value on the 12th day. Additionally, two of six animals with total splenectomy died after the 5th day postoperatively. In pigs with splenic autotransplants, PON1 activity was significantly decreased ($P < 0.05$) on the 5th, 12th, 26th and 40th days compared to the value before surgery. Comparing PON1 activity in splenectomized and autotransplanted pigs with the values in the sham-operated on the same day, PON1 activity was significantly decreased in splenectomized pigs on the 12th and 40th days compared to the sham-operated. In autotransplanted pigs, PON1 activity was significantly decreased on the 12th, 26th and 40th days postoperatively compared to sham-operated pigs (Table 1).

Lipid status. Total cholesterol concentrations in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants is shown in Table 2. In sham-operated pigs, total cholesterol was significantly decreased only on the 12th day postoperatively ($P < 0.05$) compared to the value before surgery. In splenectomized pigs, total cholesterol was significantly lower on the 5th ($P < 0.05$), 12th ($P < 0.001$), 26th

($P < 0.05$) and 40th ($P < 0.001$) days postoperatively than before surgery with the lowest value on the 12th day. In pigs with autologous splenic transplants, total cholesterol was significantly lower on the 12th, 26th and 40th days after surgery ($P < 0.05$, respectively) than before surgery. Compared to sham-operated pigs on the same day, total cholesterol was significantly decreased in splenectomized pigs on the 12th and 40th days and in the autotransplanted on the 40th day (Table 2).

Table 1. PON1 activity (U/L) in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants. All values are presented as mean \pm SEM.

	Before surgery	Days after surgery				
		1 st	5 th	12 th	26 th	40 th
Sham-operation	8.0 \pm 1.0	8.3 \pm 0.2	6.5 \pm 0.5	6.6 \pm 0.6	7.3 \pm 0.5	7.6 \pm 0.6
Splenectomy	7.0 \pm 0.3	7.0 \pm 0.5	5.0 \pm 0.5 ^a	3.5 \pm 0.5 ^{a,b}	5.7 \pm 0.4	4.0 \pm 0.4 ^{a,b}
Autotransplantation	7.4 \pm 0.5	6.6 \pm 0.9	5.0 \pm 0.5 ^a	4.8 \pm 0.5 ^{a,b}	5.1 \pm 0.4 ^{a,b}	5.1 \pm 0.5 ^{a,b}

^a $P < 0.05$ statistical difference with respect to the value before surgery; ^b $P < 0.05$ statistical difference with respect to the value in sham-operated pigs on the same day of the experiment

Table 2. Total cholesterol concentration (mmol/L) in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants. All values are presented as mean \pm SEM.

	Before surgery	Days after surgery				
		1 st	5 th	12 th	26 th	40 th
Sham-operation	2.4 \pm 0.1	2.1 \pm 0.1	2.1 \pm 0.1	1.7 \pm 0.1 ^a	2.1 \pm 0.2	2.1 \pm 0.05
Splenectomy	2.5 \pm 0.2	1.9 \pm 0.03	1.8 \pm 0.2 ^a	0.8 \pm 0.1 ^{a,b}	1.8 \pm 0.1 ^a	1.1 \pm 0.2 ^{a,b}
Autotransplantation	2.4 \pm 0.4	2.3 \pm 0.2	2.1 \pm 0.1	1.6 \pm 0.1 ^a	1.6 \pm 0.2 ^a	1.3 \pm 0.1 ^{a,b}

^a $P < 0.05$ statistical difference with respect to the value before surgery; ^b $P < 0.05$ statistical difference with respect to the value in sham-operated pigs on the same day of the experiment

Table 3. HDL-C concentration (mmol/L) in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants. All values are presented as mean \pm SEM.

	Before surgery	Days after surgery				
		1 st	5 th	12 th	26 th	40 th
Sham-operation	1.1 \pm 0.1	0.7 \pm 0.03 ^a	0.7 \pm 0.05 ^a	0.6 \pm 0.1 ^a	0.8 \pm 0.1 ^a	0.9 \pm 0.04 ^a
Splenectomy	0.9 \pm 0.1	0.6 \pm 0.0 ^a	0.6 \pm 0.1 ^a	0.3 \pm 0.1 ^{a,b}	0.8 \pm 0.1	0.4 \pm 0.1 ^{a,b}
Autotransplantation	0.8 \pm 0.1	0.7 \pm 0.1	0.6 \pm 0.05	0.5 \pm 0.1	0.5 \pm 0.1 ^b	0.5 \pm 0.1 ^b

^a $P < 0.05$ statistical difference with respect to the value before surgery; ^b $P < 0.05$ statistical difference with respect to the value in sham-operated pigs on the same day of the experiment

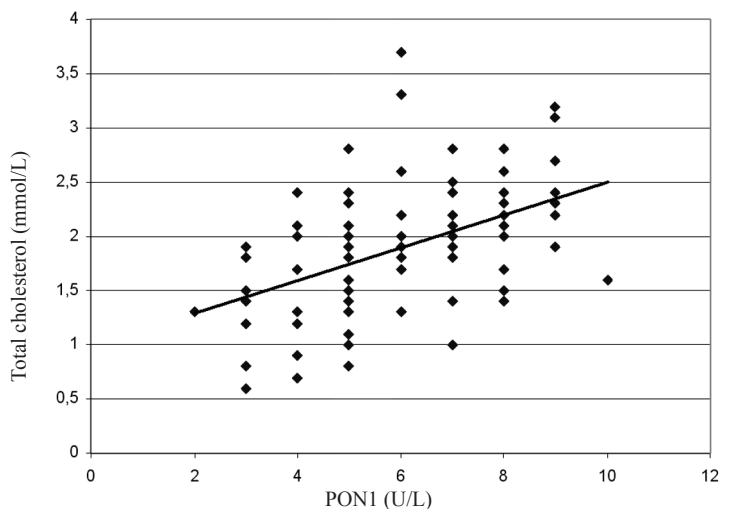


Fig. 1. Correlation between PON1 activity and total cholesterol concentration in all samples ($r = 0.476$; $P < 0.001$)

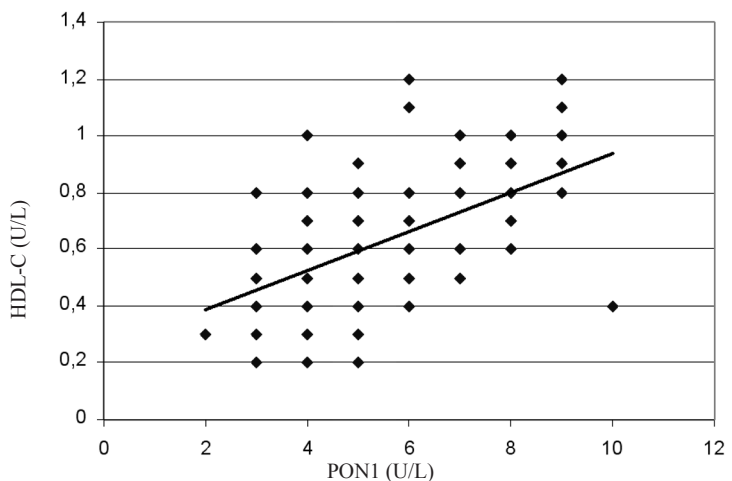


Fig. 2. Correlation between PON1 activity and HDL-C concentration in all samples ($r = 0.561$; $P < 0.001$)

HDL-C concentrations in sham-operated pigs (control group), splenectomized pigs and in pigs with autologous splenic transplants is presented in Table 3. In sham-operated pigs HDL-C was significantly decreased postoperatively, i.e. on the 1st, 5th ($P < 0.05$,

respectively), 12th ($P < 0.001$), 26th and 40th ($P < 0.05$, respectively) days, with the minimum value on the 12th day. After total splenectomy HDL-C was also decreased on the 1st, 5th ($P < 0.05$, respectively), 12th and 40th ($P < 0.001$) days, while the lowest value was on the 12th day. There were no statistical differences in HDL-C concentration in pigs with spleen autotransplant before and after surgery ($P < 0.05$). Compared to sham-operated pigs on the same day, HDL-C was significantly decreased in splenectomized pigs on the 12th and 40th days and in the autotransplanted on the 26th and 40th days (Table 3).

Correlation between PON1 activity and concentrations of total cholesterol and HDL-C. The correlation between PON1 activity and lipid parameters was examined on the pooled samples. A significant positive correlation was found between PON1 activity and total cholesterol ($r = 0.476$, $P < 0.001$, Figure 1) as well as between PON1 activity and HDL-C ($r = 0.561$, $P < 0.001$, Fig. 2).

Discussion

The beneficial effects of spleen autologous transplantation on the immunoprotective function of the splenic autotransplants against infection and inflammation have been documented (PATEL et al., 1982; LEEMANS et al., 1999; MARQUES et al., 2003). Surgical manipulation by itself evokes a cascade of inflammatory reactions in the host, well known as the acute phase response (APR) that could be accompanied by a depression in immune function (SIDO et al., 2004). Among many metabolic responses, the APR is associated with alterations in lipid and lipoprotein metabolism and oxidative stress (KHOVIDHUNKIT et al., 2004).

The present study demonstrated serum lipid alterations and PON1 activity changes in pigs after surgery. Serum total cholesterol and HDL-C were decreased after surgery in all experimental groups, regardless of the surgical procedures (sham-operation, total splenectomy and spleen autotransplantation), although the decrease was more manifested in pigs with total splenectomy and spleen autotransplantation implying that surgical trauma elicits APR and alterations of lipid and lipoproteins metabolism related to a degree of tissue lesion and trauma. Previous studies also demonstrated that inflammation/infection decreases serum cholesterol in primates as a result of a decrease in both HDL-C and LDL-C (SAMMALKORPI et al., 1988; GRUNFELD et al., 1992). Both cholesterol and HDL-C concentrations were lowest on the 12th day suggesting that this was the period of the most intensive metabolic response after surgery. FEINGOLD et al. (1998) found a reduction of serum PON1 activity during APR induced by pro-inflammatory compounds, such as LPS, TNF and IL-1, and this decrease in PON1 activity was dose-dependent. Accordingly, our results demonstrate decreased PON1 activity after total splenectomy and spleen autotransplantation indicating the relationship between post-surgical inflammation and reduced PON1 activity. The changes in PON1 activity were in accordance with an

alteration in serum lipids which is supported by the significant positive correlation of PON1 activity with both the total cholesterol and HDL-C concentrations. As opposed to results obtained previously in our lab in bovine and human sera (JURETIĆ et al., 2001; TURK et al., 2004, 2005a, 2005b, 2008), the values of PON1 activity in porcine serum was much lower compared to humans and cattle.

In conclusion, the results demonstrate decreased PON1 activity and alteration in the total cholesterol and HDL-C concentrations after surgery, due to surgical trauma that evokes inflammatory cascade and APR. Since there are no previous reports addressing PON1 activity in pigs, further studies are needed to establish the role of PON1 in porcine pathophysiology.

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SAŽETAK

Cilj je ovoga rada bio istražiti aktivnost PON1 te lipidni status u serumu svinja nakon splenektomije i autotransplantacije slezene u namjeri da se procijeni učinak stresa i traume na aktivnost PON1 i metabolizam lipida u tijeku kirurškoga zahvata. U istraživanje je bilo uključeno 19 prašćića koji su nasumično bili raspodijeljeni u tri skupine: (1) laparoskopija s intaktnom slezenom (n = 6), (2) splenektomija (n = 6) i autotransplantacija slezene (n = 7). Uzorci krvi uzimani su neposredno prije kirurškoga zahvata, te 1., 5., 12., 26. i 40. dan nakon operacije. U serumu je određena aktivnost PON1, te koncentracija ukupnoga kolesterola i HDL-kolesterola. Aktivnost PON1 bila je značajno snižena postoperativno u splenektomiranih (5., 12. i 40. dan) i autotransplantiranih životinja (5., 12., 26. i 40. dan), dok u skupini u kojoj je učinjena laparoskopija nije bilo značajnih razlika u aktivnosti PON1 nakon operacije. U skupini podvrgnutoj laparoskopiji, ukupan kolesterol bio je značajno manji samo 12. dan nakon operacije, dok je HDL-C bio manji 1., 5., 12., 26. i 40. dan postoperativno s najmanjom vrijednošću 12. dan. U splenektomirane prasadi, ukupan kolesterol bio je značajno manji 5., 12., 26. i 40. dan postoperativno, a HDL-C je bio manji 5., 12. i 40. dan nakon operacije. U prasadi kojoj je autotransplantirana slezena, ukupni je kolesterol bio značajno manji 12., 26. i 40. dan nakon operacije, dok se koncentracija HDL-C nije značajno razlikovala prije i nakon operacije. Rezultati pokazuju smanjenu aktivnost PON1 i promjene koncentracija ukupnog kolesterola i HDL-C uzrokovane kirurškom traumom i upalnim odgovorom nakon operacije.

Cljučne riječi: paraoksonaza, lipidi, serum, splenektomija, autotransplantacija slezene, kirurška trauma, upala
