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Effects of in-feed zeolite treatment on some biomarkers in dairy cows with subclinical mastitis

Dražen Đuričić[1,2,*], Silvijo Vince[2], Nino Maćešić[2], Damjan Gračner[2], Mislav Kovačić[3], Ivan Folnožić[2], Sonja Perkov[4], Marko Samardžija[2]

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Abstract

This study aims to investigate the effect of in-feed clinoptilolite treatment on biomarkers such as serum amyloid A (SAA), haptoglobin, apolipoprotein A–I (APO A–I), and paraoxonase-1 (PON1) activity, triglycerides (TRIG) and high-density lipoprotein cholesterol in dairy cows with subclinical mastitis. A total of 69 Holstein dairy cows, aged 2–7 years, kept on a farm in North-Western Croatia, were included. Cows were randomly assigned into three groups: (1) Clinoptilolite (CPL) group with subclinical mastitis (n = 20), treated in-feed 50 g natural powdered clinoptilolite twice daily from 270th day of pregnancy to the end of study; (2) nontreated cows (n = 19) with subclinical mastitis (SCM); and (3) the control group (CON) of healthy cows (n = 30). Blood samples were taken: on the day of calving and on days 5, 12, 19, 26, 33, 40, and 60 after parturition. The concentration of SAA was highest in the SCM group (p < 0.001). PON1 activity was statistically significantly lower (p < 0.001) in cows from the SCM group than in the CPL and CON groups. Decreased PON1 activity and increased APO A–I were observed in the case of SCM. The positive effect of the addition of vibroactivated clinoptilolite in the feed of treated cows resulted in reduced values of APO A–I, SAA, and haptoglobin, and higher activity of PON1 during the two-month period of lactation after calving, on the basis of which we can assume that they may be less sensitive to infection in SCM.

Keywords: *apolipoprotein A–I, dairy cows, haptoglobin, paraoxonase-1, serum amyloid A, subclinical mastitis*

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1. Introduction

From an economic point of view, inflammation of the mammary gland or mastitis in cows is the most important disease in modern dairy production. The losses are manifested through reduced milk production, costs of medicines and treatment, costs of veterinary services, increased culling rate, reduced value of discarded milk, and reduced fertility [1–3]. Detection of clinical mastitis is relatively easy, but subclinical mastitis (SCM) is difficult to detect due to the absence of visible signs of inflammation. The diagnosis of SCM was based on a positive mastitis test, an increased number of somatic cells in the milk, and confirmed by positive microbiological findings [4, 5].

Inflammation is a standard protective reaction of the organism [6, 7], which includes the production of oxygen radicals (O_2–, OH–, NO–, and hypochlorite radicals), phagocytic mechanisms, secretion of antimicrobial substances, fibrosis and neovascularization, and changes in the tissue structure of the affected part of the organism [6, 7]. Proteins in the blood that participate in maintaining homeostasis and controlling the multiplication of microorganisms before the host organism develops specific immunity are acute-phase proteins (APPs). Their concentrations vary under the influence of inflammation, trauma, and infection [8, 9]. Research in domestic animals led to the identification of several APPs previously described in humans and in laboratory animals, and differences in the acute-phase response of individual APPs between different animal species were observed [9, 10]. C-reactive protein is the main protein of the acute phase in humans, dogs, and pigs, while in ruminants its level does not increase significantly during infections or inflammation [10–15].

Haptoglobin is a protein that belongs to the α-globulin fraction and is one of the main APPs in ruminants that can be increased 100 times during the acute-phase response. It has an important role in creating immunity against infection, inflammation, trauma, and tissue damage [10, 16, 17]. In addition to haptoglobin, the main APPs of cattle include serum amyloid A (SAA), ceruloplasmin, fibrinogen, and fetuin [18, 19].

[1]Mount-trade d.o.o., Industrijska 13, 43280 Garešnica, Croatia.
[2]Clinic of reproduction and Obstetrics, Faculty of Veterinary Medicine, University of Zagreb, Heinzelova 55, 10000 Zagreb, Croatia.
[3]Department of Biology, University of Osijek, 31000 Osijek, Croatia.
[4]Merkur University Hospital, Zajčeva 19, 10000 Zagreb, Croatia.
*email: dduricic19@gmail.com

Serum amyloid A (SAA) is a small hydrophobic protein found in the blood bound to high-density lipoproteins (HDLs). Serum amyloid A is an apolipoprotein that affects the transport of cholesterol and HDLs, participates in endotoxin detoxification, inhibits the proliferation of lymphocytes and endothelial cells, and acts as a chemoattractant [20–22]. Serum amyloid A has great diagnostic value in ruminants and can be used to assess the health status of the herd and detect subclinical diseases [23]. Determination of SAA in cattle is a much more useful indicator in differentiating acute from chronic inflammatory processes than the number of neutrophils, and it is considered a reliable marker of acute inflammation [24].

For efficient energy production, cellular metabolism requires oxygen; however, reactive oxygen species (ROS) are produced, coupled with a decreased antioxidative defence and the consequent oxidative stress [25]. The increased production of free oxygen radicals damages many vital functions, which include oxidative damage to macromolecules such as lipids, proteins, and DNA, but antioxidant mechanisms, which are partly related to enzyme activities, remove and repair the resulting damage [26]. Every organism is protected from the harmful effects of reactive oxygen compounds by a widespread antioxidant system that slows down or completely prevents oxidation or removes oxidative damage [27]. An important role in the group of antioxidants that breaks down oxidation products is played by the antioxidant enzymes paraoxonase-1 (PON1), platelet-activating factor acetylhydrolase (PAF-AH), and lecithin-cholesterolacyl transferase (LCAT), which cleave lipid hydroperoxides that are formed during the oxidative changes of lipoproteins and thereby slow down the oxidative changes of lipoproteins [28].

Paraoxonase-1 is a calcium-dependent esterase that is synthesized in the liver of mammals and in serum it binds with its hydrophobic amino end to HDL phospholipids [29]. Paraoxonase catalyzes the hydrolysis of a wide range of substrates such as lipid hydroperoxides created on low-density lipoproteins (LDL). Paraoxonase-1 is an antioxidant enzyme that hydrolyzes lipid peroxides during oxidative stress [30, 31].

The anti-inflammatory and antioxidant protein apolipoprotein A–I (APO A–I) is associated with HDLs involved in lipid metabolism, and its purpose is to protect lipids from oxidation [32].

This study aims to investigate the effect of dietary vibroactivated clinoptilolite supplementation on certain APPs and oxidative stress such as SAA, haptoglobin, apolipoprotein A–I, and paraoxonase-1 activity in dairy cows with SCM.

2. Materials and methods

2.1. Animals and housing

A total of 69 dairy cows of the Holstein Friesian breed, between 2 and 7 years of age, were included in this study. They were housed and kept on the Pleško family farm near Đurđevac in Koprivnica–Križevci County, Croatia (coordinates 45°59′ N, 17°03′ E). Cows were randomly assigned into three groups: Clinoptilolite (CPL) group with subclinical mastitis that received CPL in-feed (n = 20), i.e., 50 g natural powdered zeolite clinoptilolite modified by vibroactivation and micronization (Vibrosorb®, Viridisfarm, Podpićan, Croatia) twice daily from 270th day of pregnancy to the end of observation; second (SCM) group of nontreated cows with SCM (n = 19); and the control group of healthy nontreated cows (n = 30). The CPL and SCM groups were composed of cows with a positive California mastitis test and somatic cell count above 200,000/mL (DeLaval cell counter). There weren't significant differences in milk yield between the groups of cows. All cows with clinical mastitis, metritis, lameness, milk fever, abomasal displacement, retained placenta, and cystic ovarian dysfunction were excluded from the trial. The cows were fed a ration composed of haylage, corn silage, hay, and a complete feed mixture for lactating cows with 19% of crude protein. Cows were housed in a free-stall barn with straw bedding. Drinking water was available *ad libitum*.

2.2. Ethical approval

Ethical approval for the study was obtained from the Ethical Committee of the Faculty of Veterinary Medicine, University of Zagreb, Croatia. The research protocol and animal management were in compliance with the Directive 2010/63/EU of the European Parliament (2010) on the protection of animals used for scientific purposes.

2.3. Blood sampling

Blood samples were taken after the morning milking with the BD Vacutainer® blood collection system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) from the tail vein into tubes without an anticoagulant but with a clot activator. After clotting at room temperature for 1 h, blood samples were centrifuged at 1500 × g for 15 min. Sera were separated and stored at −70 °C until analysis. For determination of certain acute-phase response and antioxidative biomarkers, samples were taken eight times as follows: on the day of calving and on days 5, 12, 19, 26, 33, 40, and 60 after parturition.

2.4. Analytical procedures

Serum triglycerides (TRIG) and high-density lipoprotein cholesterol (HDL-C) were determined by standard commercial reagent packages (Beckman Coulter Biomedical Ltd., O'Callaghans Mills, Ireland) with the Beckman Coulter AU 680 biochemical analyzer (Beckman Coulter Biomedical Ltd. München, Germany). PON1 activity was assayed spectrophotometrically at 37 °C by the paraoxon (O,O-diethyl-O-p-nitrophenylphosphate; Sigma Chemical Co., London, UK) hydrolysis method. Serum was added in the reaction mixture of 0.1 M Tris-HCl buffer, pH 8.0 containing 2.0 mM of paraoxon (O,O-diethyl-O-p-nitrophenylphosphate; Sigma Chemical Co, London, UK), 2.0 mM of CaCl, and 1 mM of NaCl at 37 °C. The absorption of the released p-nitrophenol was determined at 405 nm by the use of the Beckman Coulter AU 680 (Beckman Coulter Biomedical Ltd.) automated analyzer. Serum APO A–I concentration was measured by the quantitative ELISA method using the commercial Bovine Apolipoprotein A–I test kit (Novatein Biosciences, Cambridge, MA, USA) with the Microplate Reader DV 990BV4 (Lab services, Italy). SAA concentrations were determined by ELISA assay with a monoclonal antibody specific for SAA (Phase Range Multispecies SAA ELISA kit, Tridelta Development Ltd., Greystones, Ireland). Sera haptoglobin concentrations were determined by colorimetric assay (PHASE Haptoglobin Assay, Tridelta Development Ltd., Greystones, Ireland) according to standard procedures.

2.5. Statistical analysis

Statistical analyses were performed with the Analysis of Variance (ANOVA). The following statistical parameters are presented from the obtained results: mean value and standard error. Statistically significant differences between individual groups were calculated by Kruskal–Wallis test. The linear correlation between the investigated parameters was determined by Pearson's correlation

coefficient. Differences between individual groups were considered statistically significant at $p < 0.05$.

3. Results

Mean values (M ± S.E.M.) of apolipoprotein A–I (APO A–I), PON1, SAA, haptoglobin (HAPTO), TRIG, and high-density lipoprotein cholesterol (HDL-C) during the first 60 days of lactation in dairy cows in the control group (CON), in cows with SCM untreated, and treated with CPL are shown in **Table 1** (**Figure 1**).

Between the CPL and CON group of cows, there was no statistically significant difference ($p > 0.05$) in total PON1 activity. Paraoxonase-1 activity was statistically significantly lower ($p < 0.001$) in dairy cows from the SCM group than in the CPL and CON groups (except during second sampling it was the lowest in the CON group ($p < 0.05$)) (**Figure 2**).

The concentration of SAA was highest in the group of cows with SCM and was statistically significantly different ($p < 0.001$) from the values in the serum of cows of the CPL and CON groups. Only, during the second sampling (5 days after calving), SAA was the highest in the CON group (**Figure 3**).

No statistically significant difference was found between PON1 activity and haptoglobin concentration in the entire sample of dairy cows by correlation analysis. There was also no significant difference in PON1 activity and haptoglobin concentration in any of the investigated groups, i.e., in the control group ($r = 0.2255$; $P = 0.52$), in the group of SCM dairy cows with SCM ($r = -0.0580$; $P = 0.14$), and in the CPL group ($r = -0.6673$; $P = 0.25$). Also, there was no significant difference in APO A–I and haptoglobin concentration in the control group ($r = -0.1094$; $P = 0.44$), in the group of SCM ($r = -0.1012$; $P = 0.45$), and in the CPL group ($r = 0.1250$; $P = 0.72$). Paraoxonase-1 activity was significantly correlated with APO A–I concentration in the control group ($r = 0.9464$; $P = 0.00001$), in the group of SCM dairy cows with SCM ($r = 0.9164$; $P = 0.00014$) and in the CPL group ($r = 0.9997$; $P = 0.00076$). The concentration of TRIG was higher in cows with SCM supplemented with zeolite compared to the serum concentrations of those with SCM and lowest in healthy cows of the control group. The concentration of HDL-cholesterol was lowest in the CPL group and was statistically significantly different ($p < 0.001$) from the values in SCM and CON group of cows. Paraoxonase-1 activity was significantly correlated with HDL-C concentration in a SCM group ($r = 0.9998$; $p < 0.00001$).

Table 1 • Mean Values (M ± S.E.M.) of Apolipoprotein A–I (APO A–I), Paraoxonase-1 (PON1), Serum Amyloid A (SAA), Haptoglobin (HAPTO), Triglycerides (TRIG), and High-Density Lipoprotein Cholesterol (HDL-C) during First 60 days of Lactation in Dairy Cows in the Control Group (CON) and in Cows with Subclinical Mastitis (SCM) Untreated and Treated with Clinoptilolite (CPL)

Group: Parameter (units)	CPL	SCM	CON
	M ± S.E.M.		
APO A–I (mmol/L)	1250 ± 113.58[a]	1487 ± 78.79[a,b]	709 ± 40.53[c]
PON1 (U/L)	161.32 ±4.36[a]	136.19 ± 5.38[b]	160.56 ± 4.47[a]
SAA (mg/L)	102.1 ± 5.45[a]	141.9 ± 6.05[b]	89.6 ± 3.34[c]
HAPTO (g/L)	0.49 ± 0.24[a]	0.65 ± 0.56[b]	0.58 ± 0.37[a]
TRIG (mmol/L)	0.17 ± 0.10[a]	0.15 ± 0.09[b]	0.13 ± 0.03[c]
HDL-C (mmol/L)	2.39 ± 1.89[a]	2.55 ± 1.80[b]	2.46 ± 1.41[b]

[a,b,c]Significantly different values ($p < 0.05$) in the same row are marked with different superscript letters.

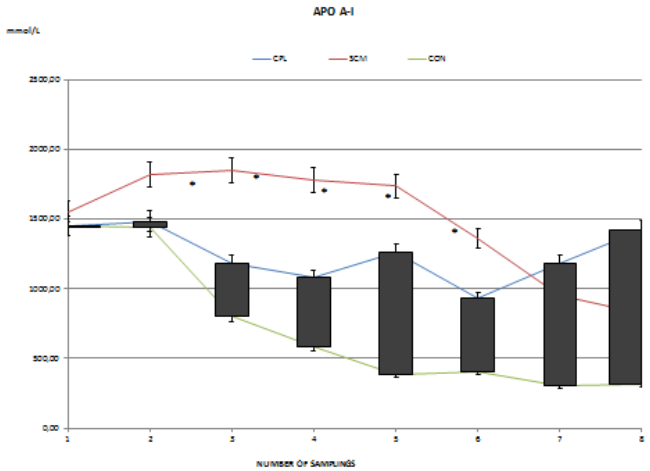

Figure 1 • Mean value of apolipoprotein A1 (APO A–I) concentration in the control group (CON) and in cows with subclinical mastitis (SCM) untreated and treated with clinoptilolite (CPL). *$p < 0.05$.

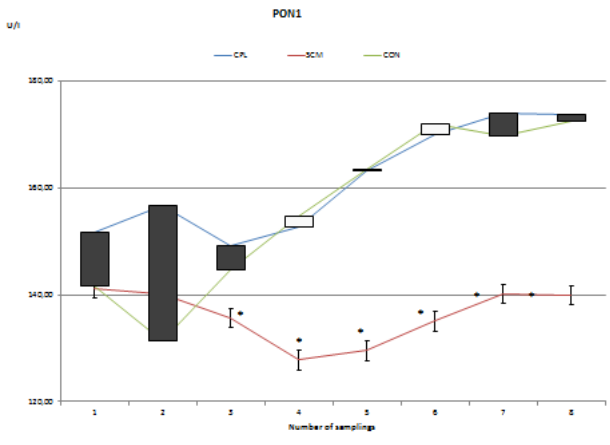

Figure 2 • Mean value of paraoxonase-1 (PON1) activity (U/I) in the control group (CON) and in cows with subclinical mastitis (SCM) untreated and treated with clinoptilolite (CPL). *$p < 0.05$.

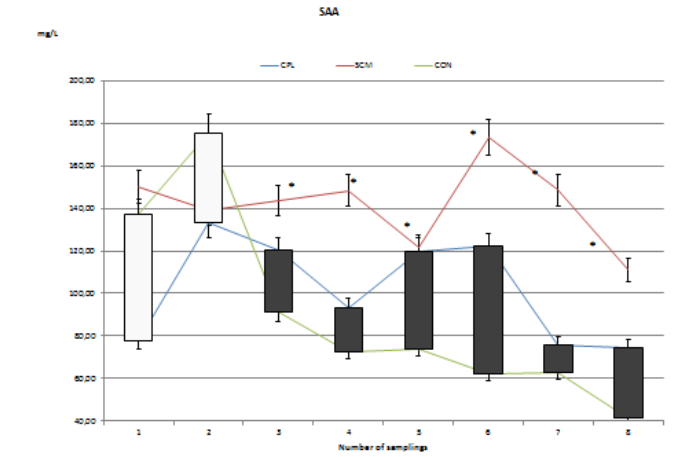

Figure 3 • Mean value of SAA concentration (mg/L) in the control group (CON) and in cows with subclinical mastitis (SCM) untreated and treated with clinoptilolite (CPL).
*$p < 0.05$.

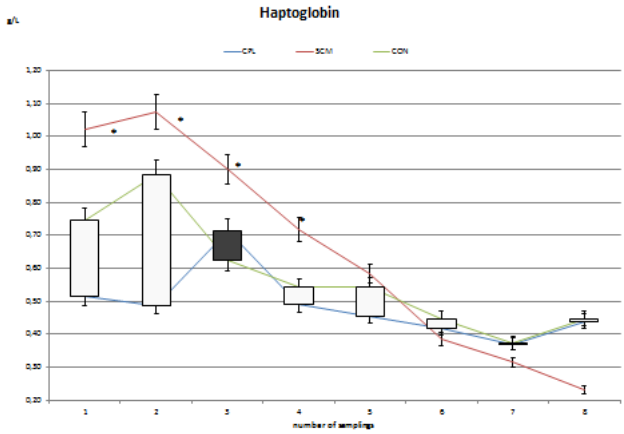

Figure 4 • Mean value of haptoglogin concentration (g/L) in the control group (CON) and in cows with subclinical mastitis (SCM) untreated and treated with clinoptilolite (CPL).
*$p < 0.05$.

4. Discussion

Low antioxidant status and oxidative stress in cows with mastitis were mentioned by Atakisi et al. [33], as well as in our study, PON1 activity was significantly lower in the SCM group of cows with SCM, compared with the CPL group that had SCM and received clinoptilolite in food and the control group (CON).

Kizil et al. [34] reported a reduced concentration of antioxidants that cleave the generated peroxides and an increased concentration of lipid peroxidation products in cows with clinical and SCM, which shows that oxidative stress is associated with inflammation. The antioxidant activity of PON1 is achieved by preventing the oxidation of lipoproteins, LDL and HDL, by breaking down biologically active lipids on oxidized LDL, by reducing the oxidation status of macrophages, and by stimulating the secretion of cholesterol from macrophages [35], while the anti-inflammatory action is reflected by monocyte chemotaxis and adhesion to endothelial cells [36] and prevention of monocyte differentiation into macrophages and expression of adhesion molecules [37]. As PON1 activity decreases during inflammation, PON1 is also considered a negative APP.

Decreased activity of PON1 and increased concentration of SAA were also found in patients with metabolic syndrome [38]. As both proteins, PON1 and SAA, are bound to HDL, during inflammation there is an increase in SAA on HDL, while the proportion of PON1 on HDL decreases [39], and there is also a decrease in the anti-inflammatory protein APO A–I on HDL, which is important for PON1 stability [40].

According to Turk et al. [41], the inflammatory response in cows affected by clinical or SCM is manifested by an increase in SAA or haptoglobin synthesis. Although Ceciliani et al. [32] claimed that a sudden increase in serum SAA concentration can only be a reliable indicator of clinical mastitis but not SCM in cows, in our study, SAA was significantly increased in the group of cows with SCM, but not in the group suffering from SCM treated with clinoptilolite. The increase in SAA levels during the first two samplings in the control group, in this study, was not caused by SCM but was assumed to be a mild uterine infection or some other unidentified inflammatory condition.

The results obtained also show that inflammation during SCM affects the lipid status, i.e., the concentration of HDL-C and TRIG. HDL-C concentration was higher in the group of cows with SCM, while triglyceride concentration was higher in cows receiving clinoptilolite. Changes in lipid status are caused by cytokines that are increased during infection and inflammation, causing changes in lipid and lipoprotein metabolism [42]. The increase in triglyceride levels during the acute-phase response probably occurs as a result of increased synthesis of fatty acids in the liver, increased lipolysis in adipose tissue, decreased oxidation of fatty acids in the liver, and decreased activity of the enzyme lipoprotein lipase [43]. It is believed that many proinflammatory cytokines such as TNF, IL-1, IL-2, and IL-6 directly affect the increase in the concentration of TRIG in the blood. Bacterial infection can affect the reduction of fatty acid oxidation in the liver, which redirects the metabolism of fatty acids to the synthesis of TRIG [42].

In this study, PON1 activity was significantly correlated with HDL-C concentration in a SCM group, indicating the association of PON1 with lipid metabolism during subclinical mammary gland inflammation.

5. Conclusions

The positive effect of the addition of vibroactivated clinoptilolite in the feed of treated cows resulted in reduced values of APO A–I, SAA, and HAPTO, and higher activity of PON1 as a negative marker, during the two-month period of lactation after calving, on the basis of which we can assume that they may be less sensitive to infection in SCM.

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Author contributions

DĐ, SV, NM, DG and MS initiated the work, devised the experiments, and supervised the study. DĐ, MK, IF, SP and MS collected and analyzed the data. ĐD, DG and MS drafted the manuscript. DĐ, IF and MK finalized the manuscript. All authors approve of this work and take responsibility for its integrity.

Conflicts of interest

The author(s) declare no conflict of interest.

Data availability statement

The data for this article can be found: project no. IP-2014-09-6601, ModZeCow.

Institutional review board statements

Ethical approval for the study was obtained from the Ethical Committee of the Faculty of Veterinary Medicine, University of Zagreb, Croatia. The research protocol and animal management were in compliance with the Directive 2010/63/EU of the European Parliament (2010) on the protection of animals used for scientific purposes.

Informed consent statement

Not applicable.

Sample availability

Not applicable.

Additional information

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