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Systemic inflammatory response and lack of preventive effect of post-partum pain medication with ketoprofen on shoulder ulcers of sows

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16 **Abstract**

17 Shoulder lesions are common in lactating sows and can affect their welfare. We assessed the
18 systemic inflammatory response to shoulder ulcers and monitored the **preventive** effect of post-
19 partum **administration** with non-steroidal anti-inflammatory medication (ketoprofen) on their
20 prevalence. In a double-blind placebo-controlled field trial, 144 YxL hybrid sows farrowing in
21 crates with a cast-iron floor received either ketoprofen (3 mg/kg) or placebo as an intramuscular
22 injection on days 0-1 after parturition. During the lactation period (weeks 1-4) all sows were
23 assessed weekly for the presence of shoulder ulcers (0 = no ulcer, 1 = unilateral ulcer, 2 = bilateral
24 ulcers; in all cases at least epithelial damage). From a subset of 37 sows, haptoglobin (Hp), albumin
25 (ALB) and cortisol (COR) were measured from blood samples taken 10 to 12 days after farrowing.
26 Results were analyzed according to a linear regression model for associations between Hp, ALB,
27 COR and shoulder ulcers. A random ordered logistic model was used to assess risk factors (body
28 condition score (BCS), back and shoulder fat, decrease in BCS or fat layer thickness during
29 lactation, parity, number of live born and stillborn piglets, piglets weaned, shoulder ulcer scar) and
30 the effect of ketoprofen treatment. Total prevalence of shoulder ulcers at lactation weeks 1-4 was
31 26.4%, 33.3%, 38.2% and 38.9%, respectively. Prevalences of unilateral shoulder ulcers at lactation
32 weeks 1-4 were 16.7%, 19.4%, 20.8% and 18.8%, and prevalences of bilateral shoulder ulcers were
33 9.7%, 13.9%, 17.4%, and 20.1%. There was a decrease in albumin and an increase in Hp levels in
34 sows with bilateral shoulder ulcers compared with sows without shoulder ulcers ($P < 0.001$) or
35 unilateral shoulder ulcers ($P = 0.014$ for ALB, $P = 0.021$ for Hp). Changes in COR levels were not
36 statistically significant **but sows with bilateral shoulder ulcers tended to have lower cortisol levels**
37 **than sows without ulcers ($P = 0.061$) and sows with unilateral shoulder ulcers ($P = 0.089$).**
38 Ketoprofen failed to protect against shoulder ulcers, but instead the treated sows had an increased
39 number of shoulder lesions at the second and third lactation week ($P = 0.023$ and $P = 0.049$).
40 **Previous shoulder ulcer was a predisposing factor for shoulder ulcers at all lactation weeks ($P <$**
41 **0.001).** Higher body condition score (BCS) and a thicker back and shoulder fat layer protected
42 against shoulder ulcers. The results indicate that bilateral shoulder ulcers trigger a systemic
43 response and should therefore be regarded as a significant finding in clinical evaluation. **Postpartum**
44 **administration of ketoprofen was ineffective in shoulder ulcer prevention.**

45 Keywords: sow, shoulder ulcer, ketoprofen, systemic response, welfare

46 **Introduction**

47 A shoulder ulcer of a lactating sow represents necrotic tissue damage of the skin and subcutaneous
48 tissue (Herskin et al., 2011). In previous studies, most from more than 10 years ago, the prevalence
49 of shoulder ulcers has been estimated to be 10-34%, with substantial variation among herds (Bonde
50 et al., 2004; Cleveland-Nielsen et al., 2004a, 2004b; KilBride et al., 2009a; Zurbrigg, 2006). Shoulder
51 ulcers are caused by long periods of pressure associated with prolonged recumbency, and are partly
52 comparable to human pressure ulcers (Jensen, 2009). During farrowing and early lactation, a sow
53 spends long periods of time lying on her side, thus placing a great proportion of her body weight on
54 the shoulder (Hötzel et al., 2004). This behavior is influenced not only by the health status of the sow
55 (Bonde et al., 2004), but also by environmental factors, such as room temperature (Malmkvist et al.,
56 2012), availability of bedding (Damm et al., 2003), and whether the sow is kept in a crate or in a
57 loose-housing pen (Blackshaw et al., 1994; Cronin et al., 1996). Davies et al. (1997) suspected that
58 periparturient conditions, especially patterns of recumbency and sow activity during farrowing and
59 early lactation, affect the development of shoulder ulcers. Predisposing factors for shoulder ulcers
60 include body condition, back fat thickness, presence of a scar from a previous shoulder ulcer and
61 flooring (Herskin et al., 2011; KilBride et al., 2009a).

62 Shoulder ulcers vary greatly in severity. They develop as a progressive process, from 'top to bottom',
63 with lesions appearing first in the skin. Necrotic tissue lesions are found in all stages of shoulder
64 ulcers, and in the most advanced form of shoulder ulcer the underlying bone (*tuber spina scapulae*)
65 is exposed and deformed (Jensen, 2009). Though clear variation in lesion severity is often clinically
66 evident, a reliable classification system for shoulder ulcers *ante mortem* has been difficult to
67 formulate.

68 Shoulder ulcers are likely to cause pain and impact sow welfare (Dahl-Pedersen et al., 2013; Larsen
69 et al., 2015). However, there is a lack of scientific data on the level of pain and inflammatory
70 responses related to shoulder ulcers (Herskin et al., 2011). Shoulder ulcers can cause extensive tissue
71 lesions with necrosis and inflammation (Jensen et al., 2014). Tissue inflammation or infection causes
72 a local tissue response that is represented with a release of cytokines and, as a consequence, acute
73 inflammatory response (Chen et al., 2003; Wang et al., 2001). As part of the acute phase response,
74 haptoglobin (Hp) is a well-established marker of tissue damage in pigs (Heinonen et al., 2010;
75 Petersen et al., 2002). Hp production is mainly regulated by cytokine levels, and their levels correlate
76 with the extent of tissue damage (Chen et al., 2003). In addition, Hp levels can increase also as a
77 consequence of physiological stress (Murata et al., 2004). Thus, as a measurable marker of

78 inflammation and stress, Hp can even act as a welfare indicator (Chen et al., 2003; Eckersall, 2000;
79 Murata et al., 2004; Piñeiro et al., 2007; Salamano et al., 2008).

80 Low albumin (ALB) levels in humans undergoing surgery, as studied by Lindgren et al. (2005),
81 represent a risk factor for pressure ulcers. In addition, Ek et al. (1991) showed that as a part of
82 nutritional status assessment, low ALB levels were related to a higher risk of pressure ulcer **in**
83 **humans**. The reason for the correlation between serum ALB levels and pressure ulcers is unclear
84 (Anthony et al., 2000). According to Ek et al. (1991), edema caused by low ALB levels could lead to
85 microcirculatory changes, and thus increase the risk for pressure ulcers. In pigs, ALB functions as a
86 negative acute phase protein, decreasing at the time of infection (Lampreave et al., 1994).
87 Accordingly, a correlation with shoulder ulcers can also be expected in sows. To our knowledge,
88 association of ALB levels with shoulder ulcers in sows has never been studied.

89 Cortisol (COR) is a traditionally used and widely researched marker of stress in various species.
90 Higher COR levels represent the activation of hypothalamic-pituitary-adrenal (HPA) axis, **which can**
91 **be induced by a large variety of disturbances in metabolic homeostasis, such as physiological stress**
92 **(Mormède et al., 2007)**. COR levels may correlate with Hp levels, reflecting different manifestations
93 of stress response in pigs (Ott et al., 2014). Furthermore, COR levels can increase as a response to
94 immunological stress, along with blood cytokine levels (Webel et al., 1997). **In sows with shoulder**
95 **ulcers, increase in cortisol levels can be expected both due to physiological stress (pain and**
96 **discomfort) and local tissue changes (necrosis and inflammation), and thus data about salivary**
97 **cortisol concentration in addition to plasma Hp levels would help to estimate the systemic response**
98 **to shoulder ulcers of varying severity.**

99 One type of pain-related behavior in animals is inactivity (Roughan and Flecknell, 2000; Short, 1998).
100 In sows, inactive lateral lying bouts cause external pressure on the shoulder tissues, decreasing the
101 blood flow and leading to tissue hypoxia and thrombosis (Lowthian, 2005; Vande Berg and Rudolph,
102 1995). The longest uninterrupted lying bouts **have been shown** to occur at the second day of lactation
103 (Rolandsdotter et al., 2009), and shoulder ulcers can start to develop during the first two days of
104 lactation (Davies et al., 1996; Rolandsdotter et al., 2009). In shoulder ulcer prevention, minimizing
105 the **duration** of external pressure **therefore seems** essential. **With administration of NSAID, we could**
106 **provide pain relief and thus prevent pain-related inactivity, which could** decrease prolonged,
107 uninterrupted lateral recumbency. Concurrently, appetite would be maintained and lactation-related
108 decrease in BCS and back fat thickness would accordingly be reduced (Viitasaari et al., 2013; Weary
109 et al., 2009). Ketoprofen is an NSAID belonging to the arylpropionic acid group. It has analgesic,

110 anti-inflammatory and antipyretic activities, and is thus indicated in pigs **within European Union** for
111 respiratory infections and Mastitis-Metritis-Agalactia (MMA) syndrome (Committee for Veterinary
112 Medicinal Products, 1996). Ketoprofen decreases the biosynthesis of peripheral prostaglandins by
113 inhibiting cycle-oxygenase enzymes, which has been considered to explain the analgesic effects of
114 ketoprofen (Kantor, 1986). However, also central mechanisms of analgesia from ketoprofen have
115 been **shown** (Cashman, 1996; Wilier et al., 1989).

116 We hypothesized that shoulder ulcers could be prevented **by administration of NSAID, that would**
117 **relieve pain associated with farrowing and early lactation**. We used ketoprofen, based on practical
118 availability and evidence of efficacy in sows (Mustonen et al., 2011). Our additional goal was to
119 assess the systemic response to shoulder ulcers by monitoring Hp, ALB, and COR levels 10-12 days
120 after farrowing, when the development of shoulder ulcers had progressed **(Davies et al., 1997)**.

121

122 **Materials and methods**

123 *Animals and housing*

124 Our study took place on a Finnish piglet-producing farm with 400 Yorkshire x Landrace first-
125 generation hybrid sows. The farm has a high health status and is clinically free of enzootic pneumonia,
126 salmonellosis, PRRS, swine dysentery (***Brachyspira hyodysenteriae***) and mange (***Sarcoptes scabiei***
127 **var. *suis***). Data were collected during one calendar year, and the study was completed in 2012. During
128 gestation, the sows were kept in gestation pens, in groups of 5 to 7 individuals. The pens contained a
129 resting area (3.5 m²/sow) with a deep bedding of peat (about 0.5 m deep) and a feeding area with a
130 concrete floor. Approximately one week (5-8 days) before expected farrowing, the sows were moved
131 into a conventional farrowing pen with a closed farrowing crate and a slatted floor. The farrowing
132 crate (width 0.6-0.7 m, length 2.4 m) had a partly slatted cast-iron floor (total width 0.63 m, total
133 length 1.96 m). The floor under the sow had a more solid area (length 97cm) at the front part of the
134 **crate**, with approximately 10% of the floor surface slatted. The floor under the front part of the sow
135 is shown in **Figure 1**. For the piglets the pen had a plastic fully-slatted floor with solid heat plates
136 (width 0.4 m, length 0.6 m). Sows were provided with a handful of hay or straw daily as rooting
137 material, piglets with peat and paper roughage. Sows were fed three times daily (at 7:00, 12:00 and
138 17:00 h) with commercial feed (Emakko-Pekoni[®], Suomen Rehu, FINLAND, NE 12.05 MJ/kg, crude
139 protein 15.5%, 2-2.9 kg/day). Water was freely available from a drinking nipple, minimum flow of 4
140 liters / minute. From one week of age the piglets were provided **with commercial piglet feed (Junior-**

141 Nasu[®], Suomen Rehu, FINLAND) for ad libitum intake. The room temperature of each farrowing
142 unit was recorded on a weekly basis (digital temperature probes, in-built farm system). Average
143 ambient temperature (all groups, all lactation weeks) was 22.9°C, with a range of 21.1-25.4°C. Piglets
144 were weaned at 4 weeks (average age 25 days; minimum 19 days, maximum 29 days). At weaning,
145 the sows were moved into insemination crates with a concrete floor for heat detection and
146 insemination, and kept in the crates for 3 to 4 weeks, until pregnancy was verified. The Finnish
147 National Animal Experiment Board (ESAVI/3331/04.10.03/2011) approved the study protocol.

148

149 *Study design*

150 We performed a double-blind, placebo-controlled clinical field trial. The study included all farm sows
151 expected to farrow at the time of the study, excluding those that showed signs of systemic illness
152 (apathy, lameness, decreased appetite) in prepartum clinical assessment. In total, 153 sows (20 first
153 parity, 133 second or greater parity) were included in the study. The calculated sample size was 70
154 in each treatment group (placebo and ketoprofen). Calculations were based on the hypothesis that
155 differences in shoulder ulcer (unilateral or bilateral) prevalence between control and ketoprofen
156 groups were at least 25% (two-sided P level at 0.05 and a study power of 80%). Sows were divided
157 based on their expected farrowing date into ten farrowing batches with batch size ranging from 11-
158 18 sows (average 14). The division of sows into farrowing batches was done according to the usual
159 practice of the farm, with no influence from the study plan. Results from nine sows were excluded
160 from the analysis because of missing data. Of those nine sows, three from the ketoprofen group died
161 due to unknown cause during the study: one sow from batch 6 at lactation week 2 and two sows from
162 batch 8 at lactation weeks 1 and 4. Six sows, four from ketoprofen group and two from placebo, were
163 relocated before the end of lactation, based on farm management that was not affected by the study
164 plan. Of those sows, data were missing from the last (4th) lactation week. On 3rd lactation week, four
165 of the sows did not have a shoulder ulcer, one had unilateral shoulder ulcer, and one had a bilateral
166 shoulder ulcer.

167 Sows in each farrowing batch were randomly divided into two treatment groups (ketoprofen vs.
168 placebo). Treatment group was marked with blue and red colored paper sheets (blue = ketoprofen and
169 red = placebo). At batch randomization we had one paper sheet for each sow; half of the paper sheets
170 for the batch were blue and half were red, and they were manually randomly mixed. After mixing,
171 the paper sheets were randomly distributed to the sows in the batch, and treatment group was

172 thereafter indicated with a color-coded paper sheet on the farrowing crates. The farmer, who
173 performed the medications according to the color codes, was blind to the medication group the sow
174 had been allocated to.

175 Sows were medicated for two days with either ketoprofen (3 mg/kg bw, Ketovet 100 mg/mL, Richter
176 Pharma AG, Austria) or placebo (isotonic saline), administered as an intramuscular injection in the
177 neck, approximately 5 cm caudally from the ventral base of the ear. The first injection was given
178 when the sow had farrowed or when the onset of farrowing was noted, between 07:30 to 16:00 h
179 (normal working hours). The second injection was given during the same normal working hours,
180 maintaining 24 hours between injections.

181

182 *Assessment of the sows*

183 All sows were examined approximately one week before expected farrowing (average 3 days,
184 minimum 0 days, maximum 10 days), to measure the fat layer in the back and in the shoulder, to
185 evaluate body condition score (BCS) and to assess shoulder ulcer scars. Scars were gauged on scale
186 0/1; 0 = no scar (healthy skin with no epithelial lesions or only lesions from a clearly different origin,
187 for example fight marks), 1 = scar (epithelial lesion with thickening and visual evidence of fibrous
188 connective tissue or granulation tissue in the skin on top of *tuber spina scapulae*) in one or in both
189 shoulders. Assessments were performed blind regarding the medication group.

190 The fat layer measurements were performed with an ultrasonic measuring appliance (P2, Renco lean-
191 meater[®], Renco corporation, Minneapolis, USA). Back fat layer was measured at the level of the last
192 rib, 6 cm to either side of the spine. The shoulder fat layer was measured from the left shoulder, above
193 the *tuber spina scapulae*, 5 cm dorsally from the *acromion*. Measurement was performed on top of
194 healthy skin, avoiding possible ulcer-, or scar-related tissue changes. During measurement, the sow
195 was either standing or sitting.

196 The evaluation of the BCS was done manually, as described by Bonde et al. (2004), but with the
197 modification of assigning also half points (scale from 1-5, with an accuracy of 0.5). BCSs were
198 evaluated by two researchers, whose consistency and agreement were tested before the study.

199 During lactation weeks 1-3, all sows were assessed once weekly for shoulder ulcers, on a 0/1/2 scale
200 (0 = no ulcer, 1 = unilateral ulcer with at least epithelial damage, 2 = bilateral ulcer with at least
201 epithelial damage in both shoulders).

202 At weaning (lactation week 4), in addition to shoulder ulcer assessment as described for lactation
203 weeks 1-3, back and shoulder fat measurements, and evaluation of BCS were repeated as before
204 farrowing.

205 Farrowing information (parity, number of piglets born, number of piglets weaned) was recorded.
206 Farm personnel recorded the number of live born and stillborn piglets based on their observations
207 within routine farm management. Cross-fostering was performed within the first 24 hours after birth
208 in order to match litter size with the number of functional teats. A newborn piglet was recorded as
209 born still if lacking breathing and moving activity within 15 minutes of birth.

210

211 *Acute phase proteins and cortisol*

212 We took stratified blood samples from a subset of 37 sows, from three different farrowing
213 batches. The stratification was based on previous randomization (ketoprofen /placebo). We aimed to
214 take half of the sampled sows in each batch so that they were previously medicated with
215 ketoprofen and the other half of them with placebo. In addition, sows were visually assessed for
216 occurrence of shoulder ulcers at the time of the sampling. Those sows were then included based on
217 presence of shoulder ulcers (shoulder ulcer score 0 / 1; 0 = no ulcer, 1 = uni- or bilateral ulcer), so
218 that the samples would contain both scores on a 50%/50% basis. Samples were taken approximately
219 12 days after farrowing, with a range of 4 to 14 days (average 10.5 days, median 11 days). Variation
220 in the sampling date originated from practical reasons, since the sows were assessed once weekly.
221 Sampling time was the same for all groups, between feedings of 12:00 h and 17:00 h. Samples were
222 taken from the coccygeal vein in the tail, with an open method into EDTA-tubes (Becton, Dickinson
223 and Company, Franklin Lakes, NJ, USA), centrifuged (1 900 g, 15 minutes) and kept frozen (-18°C)
224 until analysis.

225 The serum samples were analyzed for ALB, Hp, and COR. ALB was analyzed using a colorimetric
226 method with an automated clinical biochemistry analyzer (Spotchem EZ SP-4430, Arkray, Kyoto,
227 Japan), following the manufacturer's instructions for analysis of porcine serum. Hp was analyzed
228 using a hemoglobin-binding method described for cows (Makimura and Suzuki, 1982).
229 Tetramethylbenzidine was used as a chromogen (Alsemgeest et al., 1994), with a 5 µg sample volume
230 (originally 20 µg). The assay results were read at 450 nm using a spectrophotometer (SUNRISE,
231 Tecan, Männedorf, Switzerland). Pooled and lyophilized aliquots of porcine acute phase serum were
232 used to create standard curves by serial dilutions. The standard was calibrated using a porcine serum

233 sample of known Hp concentration provided by the European Commission Concerted Action Project
234 (number QLK5-CT-1999-0153). The standard curve range was 0.254-4.06 g/L. A commercially
235 available RIA kit (Orion Diagnostica, Spectria®, Espoo, Finland, coated tube radioimmunoassay)
236 was used with modifications to measure cortisol in porcine plasma. Analysis was done as previously
237 validated for pigs by Oliviero et al. (2008).

238

239 *Statistics*

240 Linear regression models were used to explore different (no ulcers, unilateral ulcers, and bilateral
241 ulcers) shoulder ulcer effects on the sow inflammatory response. Hp, albumin, and cortisol were
242 included in those models as response variables. Models initially included sow variables (parity,
243 piglets weaned, number of still born and live born piglets, sampling day interval from parturition to
244 sampling day, BCS, back fat (mm), and shoulder fat (mm) before farrowing and at weaning), shoulder
245 ulcers (no ulcers, unilateral ulcers, and bilateral ulcers), and farrowing group as explanatory variables.
246 Backward elimination was performed for the final models. Farrowing group was retained in all
247 models as a potential confounding factor. The model assumptions were verified by scatter and
248 normality plots of standardized residuals, and logarithmic transformation of Hp and square root
249 transformation of cortisol were used.

250 A random-ordered logistic model was used to explore risk factors (BCS, back and shoulder fat,
251 decrease in BCS or fat layer thickness during lactation, parity, number of live born and stillborn
252 piglets, piglets weaned, shoulder ulcer scar) for shoulder ulcers and effects of ketoprofen treatment
253 after farrowing on the presence of shoulder ulcers during lactation. An ordered logistic model was
254 chosen because bilateral shoulder ulcers showed a clearly stronger inflammatory response (higher Hp
255 and lower albumin) than unilateral ulcers, and an ordinary logistic model with two level response
256 variables (ulcers yes or no) would have underestimated the severity of shoulder ulcers. For ordered
257 logistic models, three levels of ordered dependent variables for shoulder ulcers were used (no ulcers,
258 unilateral ulcers, and bilateral ulcers). As BCS, back fat and shoulder fat were highly correlated, their
259 associations with shoulder ulcers were evaluated using separate models. To study the effect of the
260 degree of body mass decrease during the lactation period on shoulder ulcers, BCS, back fat, and
261 shoulder fat results at week four were decreased from prepartum results and used in models as
262 predictive variables. Models initially included the following explanatory variables: sow variables
263 (parity, live born and still born piglets, piglets weaned), ketoprofen treatment, presence of shoulder

264 ulcer scar prepartum, and one of body condition measured before farrowing (BCS as a four-level
265 variable: < 3.0, = 3.0, = 3.5, and > 3.5, thickness of back fat in mm, and thickness of shoulder fat in
266 mm) and decrease in body condition variables (BCS, thickness of back fat and thickness of shoulder
267 fat separately) and all those variable interactions with lactation weeks as fixed factors. Sow was
268 included as a random factor in all models to account for clustering effect. A backward elimination
269 method was used for final models. For evaluating ketoprofen effect on shoulder ulcers, a model with
270 BCS was used as a model with the most conservative association estimate between ulcers and
271 ketoprofen treatment.

272 The underlying assumption of ordered logistic regression was that the relationship between each pair
273 of outcome groups is the same (so-termed proportional odds assumption). Therefore, for a one-unit
274 change in the predictor variable, the odds for cases in a group greater than the response variable level
275 (versus one less than or equal to the level) are the proportional odds times larger. The proportional
276 odds assumption for all models was tested using a likelihood ratio test and a Brant test. As all tests
277 were non-significant, model assumptions were met. Significance level was set at $P \leq 0.05$ and **P =**
278 **0.051-0.099 was interpreted as tendency**. Results are expressed as means with \pm standard deviation
279 (SD) **or least squared means (LSMeans) \pm standard error (SE)** and odds ratios (OR) with 95%
280 confidence interval (CI).

281 STATA 11.0 (Stata Corporation, Texas, USA) software was used for all statistical analyses.

282

283 **Results**

284 Total prevalence of shoulder ulcers at lactation weeks 1-4 was 26.4%, 33.3%, 38.2% and 38.9%,
285 respectively. Prevalences of unilateral and bilateral shoulder ulcers at lactation weeks 1-4 were
286 **16.7%, 19.4%, 20.8%, 18.8% and 9.7%, 13.9%, 17.4%, 20.1%**, respectively. Prevalences by study
287 groups and lactation weeks are given in Figure 2. Scars from shoulder ulcers in previous lactation
288 periods were evident in 45.1% of the sows. Mean and SD of sow parity, number of live born and
289 stillborn piglets, number of weaned piglets, BCS, thickness of back and shoulder fat layer by study
290 groups are given in Table 1.

291 Ketoprofen failed to protect against shoulder ulcers (Table 2). There was no significant association
292 between ketoprofen treatment and shoulder ulcers at the first week after parturition. At lactation week
293 two and three, ketoprofen treated sows were predisposed to shoulder ulcers (OR 2.86, 95% CI: 1.15-

294 7.09; $P = 0.023$ and OR 2.33, 95% CI: 1.00-5.41; $P = 0.049$). Number of stillborn piglets increased
295 the risk of shoulder ulcers at lactation weeks two and four ($P = 0.033$ and $P = 0.025$; Table 2). Previous
296 shoulder ulcer (ulcer scar) was a predisposing factor for shoulder ulcers at all lactation weeks ($P <$
297 0.001 ; Table 2). Protective factors were higher BCS ($P < 0.001$; Table 2), thicker back fat layer ($P <$
298 0.001 at all lactation weeks; mean and SD are given in Table 3), and thicker shoulder fat layer ($P <$
299 0.001 at all lactation weeks; mean and SD are given in Table 3).

300 Serum Hp (Figure 3) was significantly higher ($P < 0.001$) and serum ALB (Figure 4) was significantly
301 lower ($P = 0.001$) in sows with bilateral shoulder ulcers than in sows with no shoulder ulcers.
302 Furthermore, serum Hp was higher ($P = 0.021$) and serum ALB was lower ($P = 0.014$) in sows with
303 bilateral shoulder ulcers compared with sows with a unilateral shoulder ulcer. There was a tendency
304 of lower cortisol concentrations in sows with bilateral ulcers than in sows without ulcers ($P = 0.061$)
305 and between sows with bilateral ulcers than in sows with unilateral ulcers ($P = 0.089$). Between sows
306 with no shoulder ulcer and a unilateral shoulder ulcer, there was no significant difference in serum
307 Hp, ALB or COR levels.

308 Parity, number of live born piglets, number of weaned piglets, or decrease in body condition variables
309 (decrease from parturition values to fourth lactation week values for BCS, back fat layer, or shoulder
310 fat layer, Table 2) were unrelated to the prevalence of shoulder ulcers at any lactation week.

311

312 **Discussion**

313 We failed to demonstrate a protective effect against shoulder ulcers from post-partum NSAID
314 (ketoprofen) medication. Instead of a protective effect, our results indicated that ketoprofen treatment
315 predisposes a sow to shoulder ulcers. This **unexpected** finding was, however, evident only during the
316 second and third week of lactation. Viitasaari et al. (2013) reported that sows medicated with
317 ketoprofen for 3 days after farrowing showed a slower shoulder ulcer deterioration 4 to 6 days
318 postpartum, when compared with sows treated with saline placebo. We did not assess the daily change
319 in shoulder ulcer score. However, Viitasaari et al. (2013) demonstrated that ketoprofen is unable to
320 prevent the development of shoulder ulcers; at most it slows down the progression of the condition.
321 Ketoprofen may alter pain-related behavioral response in sows, with variation in sows of different
322 parity (Viitasaari et al., 2014). It is possible that NSAID medication enables pain to be ignored, and
323 thus allows prolonged lateral recumbency, which could explain the predisposing effect of ketoprofen.

324 We established a predisposing effect on shoulder ulcers at lactation weeks 2 and 4 from an increased
325 number of stillborn piglets. This is supported by Davies et al. (1997), who found a tendency of
326 association between number of stillborn piglets and shoulder ulcer prevalence. Moreover, they
327 recorded a similar positive correlation with shoulder ulcer severity. Number of stillborn piglets is
328 positively correlated with farrowing duration (Björkman et al., 2017; Oliviero et al., 2010; Van Dijk
329 et al., 2005). Farrowing duration, especially when increasing the **duration** of uninterrupted lying
330 bouts, could affect the development of shoulder ulcers (Davies et al., 1996; Rolandsdotter et al.,
331 2009). Stillborn piglets could also reflect other health issues that would increase the risk of developing
332 shoulder ulcers, but in our study, this was not supported by clinical examination of the sows. Although
333 reasons for the correlation of shoulder ulcers and the number of stillborn piglets are unclear, in
334 shoulder ulcer prevention sows with increased numbers of stillborn piglets should receive more
335 attention and enhanced **preventive** treatment.

336 Studies addressing shoulder ulcer treatment are rare, and they mainly assess the use of rubber mats
337 or local ulcer treatment, once the shoulder ulcer has developed. In practical evaluation, efficient
338 treatment methods have been difficult to find. Zurbrigg (2006) reported a faster recovery from
339 shoulder ulcers in sows with a rubber mat placed on the floor of the farrowing crate. Furthermore,
340 Kaiser et al. (2013) found a positive treatment effect from rubber mat and local treatment with zinc
341 ointment. With careful planning (Schubbert et al., 2014), rubber mats could also be useful in shoulder
342 ulcer prevention. But, due to the multifactorial nature of shoulder ulcers, other **preventive** methods
343 should also be actively established. Even though ketoprofen was ineffective as a **preventive**
344 medication against shoulder ulcers, we believe that sows with health issues requiring analgesia (such
345 as lameness, MMA or prolonged farrowing) can benefit from appropriate ketoprofen medication.
346 This assessment is based both on practical evaluation and findings by Viitasaari et al. (2013).

347 Shoulder ulcer prevalences at lactation weeks 1-4 were consistent with numbers reported in the
348 literature (Herskin et al., 2011). Davies et al. (1996) reported much lower prevalence (8.3%) when
349 all sows in a breeding herd, regardless of their time of farrowing, were assessed. But, **they also**
350 **reported that** at the time of peak prevalence (11-20 days after farrowing), shoulder ulcers were found
351 in up to 51% of the sows. Similar results were reported by Davies et al. (1997), with 12 days after
352 farrowing shoulder ulcer prevalence reaching 48%. In our study, unilateral shoulder ulcer prevalence
353 decreased by the fourth lactation week, which is in line with previous findings on shoulder ulcer
354 healing already during lactation (Davies et al., 1997; KilBride et al., 2009b). Instead, the prevalence
355 of bilateral shoulder ulcers increased throughout the lactation from 9.7% to 20.1%. Comparable

356 results on bilateral shoulder ulcer prevalence during lactation are difficult to find; Rolandsdotter et
357 al. (2009) reported that 6/18 sows (33%) had bilateral shoulder ulcers at the time of weaning.

358 The prevalence of shoulder ulcer scars, reflecting shoulder ulcers from previous lactations, was
359 45,1%. This is considered to be relatively high, although scar prevalence is rarely reported. Davies et
360 al. (1996) described that before farrowing approximately one quarter of sows had shoulder ulcer scars.
361 To date we have limited information about the healing process of shoulder ulcers. Healing within a
362 few weeks after weaning, even without treatment, is considered normal, but there seems to be large
363 variance in the **duration** and **characteristics** of the healing process, and the most prominent type of
364 healing occurs via secondary healing (Herskin et al., 2011). The high prevalence of shoulder ulcer
365 scars in our study might be due to a cumulative effect: previous shoulder ulcer predisposes a sow to
366 shoulder ulcers at subsequent lactations. Scars may also represent a poor healing process because
367 treatment of shoulder ulcers was rare on our study farm. **Preventive methods, such as optimizing body**
368 **condition score and use of rubber mats, should be actively implemented on subsequent lactations to**
369 **sows with shoulder ulcer scars.**

370 Shoulder ulcer prevalence has shown extensive herd related variation (Herskin et al., 2011). In
371 combination with the relatively high prevalence of shoulder ulcers in our study, the high prevalence
372 **of** scars from previous shoulder ulcers might suggest a herd-related management challenge, despite
373 good general herd health. In general, our study suggests that shoulder ulcers are an active health issue
374 in the pig industry, with at best moderate decrease in prevalence during the recent decade.

375 Our results showed that bilateral shoulder lesions triggered a systemic inflammatory response in
376 sows. This response was characterized by an increase in Hp and decrease in ALB concentrations,
377 when compared to sows with unilateral shoulder ulcer or absence of ulcers. As a consequence of
378 tissue damage, this reflects previous tail biting findings by Heinonen et al. (2010), who established a
379 positive correlation **between** Hp levels and tail biting lesion severity. Correlation of systemic
380 inflammatory response and the severity of unilateral or bilateral shoulder ulcer requires further study.
381 To date, division between unilateral and bilateral shoulder ulcers is included in some studies, but this
382 division is rarely compared with the severity of the lesions. As an exception, Davies et al. (1996)
383 reported that sows with bilateral shoulder ulcers had wider lesions than sows with unilateral lesions.

384 Hp levels are mainly regulated by cytokines, that are also active in the cellular level pain transduction
385 process (Kidd and Urban, 2001). Thus, elevated Hp levels leading to the activation of pain stimulus
386 pathways represents a logical consequence. Behavioral observations support this expectation of pain:

387 Larsen et al. (2015) found that sows with shoulder ulcers showed altered behavior and decreased
388 maternal behavior, and shoulder ulcers were likely to cause pain. Therefore, even though welfare
389 aspects of shoulder ulcers have been debated, **the present study supports** the assumption of
390 endangered welfare in sows with shoulder ulcers.

391 In addition to Hp, lower ALB levels are considered to represent the inflammatory response as a
392 negative acute phase protein (Lampreave et al., 1994). However, we were unable to locate
393 information about ALB levels in sows as part of the acute phase response, especially when linked to
394 shoulder lesions. There might also be additional reasons for the negative correlation between bilateral
395 shoulder ulcers and albumin levels, such as nutritional aspects. Low albumin levels in humans can
396 lead to loss of blood oncotic pressure and tissue odema, thus increasing the risk for pressure-related
397 ulcers (Ek et al., 1991). Since odema is usually the result of severe hypoalbuminemia (Tulassay et
398 al., 1989), this mechanism should not exert a major influence on our results. Albumin loss through
399 large wounds is an acknowledged problem in humans (Lehnhardt et al., 2005), and could lead to a
400 decrease in blood albumin levels, but we consider this to be a less likely explanation for our findings.

401 Our findings emphasize the clinical relevance of shoulder ulcers, especially regarding welfare. In line
402 with increased attention towards shoulder ulcers, some countries have tightened the legislation
403 concerning shoulder ulcers, and have set limitations on transportation of sows with shoulder ulcers
404 wider than 3 cm **(Barington et al., 2016)**. In addition, **in Denmark** sows with shoulder ulcers that
405 involve the subcutaneous tissue can be handled as forensic cases (Barington et al., 2016). Based on
406 systemic inflammatory response, bilateral shoulder ulcers should receive increased attention in
407 treatment choices as well as in the general health assessment of sows. Furthermore, sows with
408 bilateral shoulder ulcers should be assessed as possibly systemically ill, both in farm management
409 and the food production chain. Inflammatory response in relation to shoulder ulcers has not been
410 studied before, and the exact pathogenesis behind this reaction requires further assessment. Many
411 factors can affect the systemic inflammatory response, such as inflammation, tissue trauma, stress
412 and infection (Murata et al., 2004). Although infection in shoulder ulcers is **intermittently** considered
413 a rare consequence, Lund et al. (2003) reported an infection accompanying up to 85% of shoulder
414 ulcers. We did not study the infection rate of shoulder ulcers in our study. Systemic inflammatory
415 response and its relation to shoulder ulcers, especially regarding lesion severity and time from
416 farrowing, should be studied in more detail for better assessment of the extent of systemic response.
417 It also seems clear that in both statistical and clinical evaluation, unilateral and bilateral shoulder
418 ulcers should be assessed as separate entities.

419 Consistent with many previous studies, our study revealed that high BCS protects from shoulder
420 ulcers. The same protective effect from a thicker back and shoulder fat layer was found. These
421 protective effects were apparent in the first week of lactation. Thus, maintaining a BCS above 3.5
422 before farrowing is vital for preventing the development of shoulder ulcers.

423

424 **Conclusions**

425 Shoulder ulcers should be assessed as a condition with possible systemic effects, emphasizing the
426 relevance of bilateral shoulder ulcers in clinical evaluation. Based on current knowledge and our
427 results, the BCS and **shoulder fat layer** of sows represent an important intrinsic factor affecting the
428 development of shoulder ulcers, **with strong predisposing effect from a previous shoulder ulcer.**
429 **Administration of NSAID in the immediate post-partum period was** ineffective for preventing
430 shoulder ulcers.

431

432 **Conflict of interest statement**

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437

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442

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610

611 **Figure 1.** Partly-slatted cast-iron floor in the farrowing crate of the 153 study sows evaluated for
612 shoulder ulcers, showing the floor in the front part of the farrowing crate, with approximately 10%
613 of the floor surface slatted.

614

615 **Figure 2.** The prevalence of sows with shoulder ulcers (0 = no ulcers, 1 = unilateral ulcers, 2 =
616 bilateral ulcers) in 144 sows treated with ketoprofen (n = 71) and with placebo (n = 73) by lactation
617 week. Numbers over columns represent number of sows in ketoprofen/placebo group respectively.

618 * Significant (P = 0.023) predisposing effect of ketoprofen evaluated by random-ordered logistic model
619 where three level shoulder ulcer groups as ordered categorical variable was used as response variable.

620 # Significant (P = 0.049) predisposing effect of ketoprofen evaluated by random-ordered logistic model
621 where three level shoulder ulcer groups as ordered categorical variable was used as response variable.

622

623 **Figure 3.** Sow serum haptoglobin (Hp) concentrations evaluated by regression according to
624 shoulder ulcer groups (no ulcers, n = 22; unilateral ulcers, n = 9; and bilateral ulcers, n = 6) in 37
625 sows 4-14 after farrowing. The graph shows back-transformed (from logarithmic scale) least
626 squared means (g/L, LSMeans) and standard errors (SE).

627

628 **Figure 4.** Sow serum albumin (ALB) concentrations evaluated by regression according to shoulder
629 ulcer groups (no ulcers (n = 22), unilateral ulcers (n = 9) and bilateral ulcers (n = 6)) in 37 sows 4-
630 14 after farrowing. The graph shows least squared means (g/L, LSMeans) and standard errors (SE).

631

632

633 **Table 1.** Sow parity, number of live born and stillborn piglets, number of weaned piglets, body
 634 condition score (BCS), thickness of back and shoulder fat layer by **treatment group (placebo or**
 635 **ketoprofen)** before farrowing (prepartum) and at weaning (postpartum).

Variable	Placebo (n = 73)		Ketoprofen (n = 71)	
	Prepartum (mean ± SD)	Postpartum/ at weaning (mean ± SD)	Prepartum (mean ± SD)	Postpartum/ at weaning (mean ± SD)
Parity		4.7 ± 3.1		4.8 ± 3.4
Weaned piglets		10.4 ± 2.1		9.8 ± 2.3
Live born piglets		10.6 ± 4.5		10.7 ± 4.4
Still born piglets		2.2 ± 2.2		1.9 ± 2.2
BCS	3.5 ± 0.8	3.2 ± 0.7	3.4 ± 0.7	3.0 ± 0.6
Back fat, mm	17.3 ± 5.6	13.7 ± 4.6	15.6 ± 5.1	12.5 ± 3.9
Shoulder fat, mm	17.3 ± 4.9	13.5 ± 3.7	16.0 ± 4.4	12.9 ± 3.2

636

637

638

639 **Table 2.** Associations of sow risk factors (number of stillborn piglets and presence of shoulder ulcer
640 scar before farrowing), body condition score (BCS) and ketoprofen treatment 0-1 days post partum
641 (3 mg/kg, IM, 1x day, 2 days) with presence of shoulder ulcers (no ulcers, unilateral ulcers or bilateral
642 ulcers) in sows (n = 144) by lactation weeks (1-4). Associations were tested using ordered logistic
643 regression model.

Variables	OR ¹	95% CI of OR	P-value	Wald test P-value
Week 1 (n = 106/24/14) ²				
Treatment group:				
placebo (n = 73)	1			
ketoprofen (n = 71)	1.66	0.65; 4.25	0.288	
Number of still born piglets	1.14	0.91; 1.42	0.255	
Ulcer scar ³ :				
no (n = 104)	1			
yes (n = 40)	9.67	3.25; 27.92	<0.001	
BCS ⁴ :				
<3.0 (n = 24)	1			
=3.0 (n = 35)	1.14	0.36; 3.11	0.912	<0.001
=3.5 (n = 33)	0.03	0.00; 0.23	0.001	
>3.5 (n = 52)	0.04	0.01; 0.16	<0.001	
Week 2 ⁵ (n = 96/28/20) ²				
Treatment group:				
placebo	1			
ketoprofen	2.86	1.15; 7.09	0.023	
Number of still born piglets	1.28	1.02; 1.61	0.033	
Ulcer scars:				
no	1			
yes	9.067	3.39; 24.16	<0.001	
BCS:				
<3.0	1			
=3.0	0.55	0.19; 1.62	0.277	<0.001
=3.5	0.02	0.00; 0.12	<0.001	
>3.5	0.02	0.00; 0.08	<0.001	
Week 3 ⁵ (n = 89/30/25) ²				
Treatment group:				
placebo	1			
ketoprofen	2.33	1.00; 5.41	0.049	
Number of still born piglets	1.16	0.94; 1.43	0.154	
Ulcer scars:				
no	1			
yes	11.62	4.62; 29.21	<0.001	
BCS:				
<3.0	1			
=3.0	0.37	0.12; 1.08	0.070	<0.001
=3.5	0.03	0.01; 0.12	<0.001	
>3.5	0.04	0.01; 0.14	<0.001	
Week 4 (n = 88/27/29) ²				

Treatment group:				
placebo	1			
ketoprofen	1.84	0.82; 4.14		0.141
Number of still born piglets	1.26	1.02; 1.53		0.025
Ulcer scars:				
no	1			
yes	8.51	3.51; 20.61		<0.001
BCS:				
<3.0	1			<0.001
=3.0	0.47	0.16; 1.37		0.167
=3.5	0.03	0.01; 0.15		<0.001
>3.5	0.06	0.02; 0.19		<0.001

644 ¹ Odds ratios from ordered logistic regression models (three level ordered response variable – no
645 ulcers, unilateral ulcers or bilateral ulcers) implies that one unit change in the predictor variable, the
646 odds for cases in a group that is greater than response variable level versus less than or equal to this
647 level are the proportional odds times larger.

648 ² Number of sows with no ulcers / unilateral ulcers / bilateral ulcers.

649 ³ Occurrence of previous shoulder ulcer.

650 ⁴ Body condition score before farrowing.

651 ⁵ Number of sows in different variables groups are the same as in lactation week 1.

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653 **Table 3.** Sows body condition score (BCS), back fat and shoulder fat data (mean \pm SD) by shoulder
 654 ulcer group (0 = no ulcer, 1 = unilateral ulcer, 2 = bilateral ulcer) and by lactation week (1-4).

Shoulder ulcer group	Prepartum (mean \pm SD)			At weaning (mean \pm SD)		
	0	1	2	0	1	2
Week 1 (n of sows)	106	24	14	106	24	14
BCS	3.6 \pm 0.7	2.9 \pm 0.6	2.6 \pm 0.6	3.2 \pm 0.6	2.7 \pm 0.6	2.8 \pm 0.6
Back fat, mm	17.9 \pm 4.6	13.8 \pm 3.6	12.4 \pm 3.4	14.2 \pm 3.1	10.8 \pm 2.4	10.1 \pm 2.4
Shoulder fat, mm	17.9 \pm 5.2	12.8 \pm 4.2	12.6 \pm 4.5	14.4 \pm 4.0	9.4 \pm 2.5	10.1 \pm 3.6
Week 2 (n of sows)	96	28	20	96	28	20
BCS	3.7 \pm 0.7	3.1 \pm 0.5	2.7 \pm 0.6	3.3 \pm 0.6	2.7 \pm 0.6	2.7 \pm 0.6
Back fat, mm	18.1 \pm 4.6	14.8 \pm 3.4	12.4 \pm 3.5	14.5 \pm 3.0	10.5 \pm 2.8	10.8 \pm 2.8
Shoulder fat, mm	18.4 \pm 5.1	13.3 \pm 4.0	12.2 \pm 4.0	14.7 \pm 3.9	10.2 \pm 3.4	9.6 \pm 2.9
Week 3 (n of sows)	89	30	25	89	30	25
BCS	3.7 \pm 0.7	3.2 \pm 0.6	2.8 \pm 0.7	3.3 \pm 0.6	2.8 \pm 0.6	2.7 \pm 0.6
Back fat, mm	18.1 \pm 4.7	15.7 \pm 4.0	12.9 \pm 3.4	14.6 \pm 3.1	11.3 \pm 2.8	10.7 \pm 2.9
Shoulder fat, mm	18.4 \pm 5.2	14.0 \pm 4.3	12.6 \pm 4.1	14.8 \pm 4.0	10.8 \pm 3.2	10.0 \pm 3.5
Week 4 (n of sows)	88	27	29	88	27	29
BCS	3.7 \pm 0.7	3.1 \pm 0.6	2.9 \pm 0.7	3.3 \pm 0.6	2.7 \pm 0.5	2.8 \pm 0.6
Back fat, mm	17.7 \pm 4.7	16.2 \pm 4.7	13.9 \pm 4.0	14.5 \pm 3.2	11.3 \pm 2.9	11.0 \pm 2.8
Shoulder fat, mm	18.1 \pm 5.3	14.9 \pm 4.9	13.1 \pm 4.4	14.8 \pm 4.0	10.5 \pm 3.3	10.6 \pm 3.5

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