# Associations between Modic changes and lower back pain in the dog

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## Abstract

**Background:** Modic changes (MC) are signal intensity changes in the vertebral endplates visible on Magnetic Resonance Imaging (MRI). In humans there is a strong association between the presence of MC's and lower back pain. MC's are also visible on MR images of dogs, however the association between the presence of these changes and lower back pain in the dog is yet undetermined.
The purpose of this study was to investigate whether there is a correlation between MC's and lower back pain in dogs.
**Material and Methods:** For this retrospective research 340 lumbar MRI's were analyzed from dogs referred for MRI during December 2013 to November 2016 to the Department of Clinical Sciences of Companion Animals, Utrecht University. These MR images were evaluated for the presence, type and severity of MC's and for the presence and grade of disc degeneration and herniation. A scoring sheet was used to determine whether the patients were experiencing low back pain at the time the MRI was performed.
**Results:** MC's are present in the canine spine with a prevalence of 77% and statistical analysis with Pearson's Chi Squared Test showed a significant predilection site on the lumbosacral junction ($p<0.001$) in comparison to other lumbar segments. Type 3 changes are the most found changes in the canine spine. Logistic regression analysis showed that protrusion of the intervertebral disc (IVD) is a risk factor for the presence of MC's on L7-S1 (<25% protrusion with OR of 2.436 [95% CI 1.339-4.433, $p=0.004$], >25%<50% protrusion with OR of 3.611 [95% CI 1.813-7.192, $p<0.001$], >50% protrusion with OR of 14.711 [95% CI 5.364-40.344, $p<0.001$] and extrusion with OR of 17.105 [95% CI 3.788-77.249, $p<0.001$]).
Predictors of disc degeneration are age (OR 1.336, 95% CI 1.199-1.488, $p<0.001$), Chondrodystrophic breeds (OR 6.229, 95% CI 2.921-13.286, $p<0.001$), >50% protrusion of the IVD (OR 5.591, 95% CI 2.039-15.327, $p=0.001$) and MC type 1 (OR 9.856, 95% CI 1.956-49.659, $p=0.006$).
No significant correlation is found between low back pain and the presence of MC's or other radiographic findings.
**Conclusion:** Modic change type 3 is a common finding on MR images of dogs with a predilection site on L7-S1. This study found that MC's are positively associated with protrusion and extrusion of the adjacent IVD. Disc degeneration has positive associations with age, chondrodystrophia, protrusion of the IVD and MC type 1. So far no correlations have been found between the presence of MC's and low back pain in the dog.

**Keywords:** Modic changes, Low back pain, Dog, Retrospective study, Endplate changes, Magnetic Resonance Imaging

## Background

*What are Modic changes?*

Modic changes (MC) are vertebral endplate changes first described by Modic *et al.* in 1988, hence the naming of these abnormalities. These vertebral endplate changes are visible on Magnetic Resonance Imaging (MRI) by changes in the signal intensity of the endplates and adjacent parts of the vertebral bodies. Modic *et al.* differentiated three different kinds of endplate abnormalities. (Modic *et al.* 1988a, Modic *et al.* 1988b)

- Type 1 Modic changes are characterized by decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. (Figure 1 a and b)
- Type 2 Modic changes have increased intensity in T1-weighted images and have the same or a slight increase in intensity on T2-weighted images. (Figure 1 c and d)
- Type 3 Modic changes are characterized by decreased signal intensity on T1- and T2-weighted images. (Figure 1 e and f)

Research showed that these types can evolve into other types and can change in extent over time. (Mitra *et al.* 2004) Type 1 MC can evolve to type 2, type 2 MC can evolve to type 3 MC and type 1 and type 2 MC can disappear over time. (Järvinen *et al.* 2015, Albert *et al.* 2007, Luoma *et al.* 2008)

A certain type of Modic changes can occur on its own but mixed types are also reported. They may present themselves focally or diffusely along the endplates but are usually linear shaped and they are always parallel to the endplates. (Zhang *et al.* 2008) The signal intensity changes are a reflection of the composition of the vertebral body marrow. Normal vertebral body marrow is composed of normal hematopoietic cells, fibroblastic tissue and fat arranged between bony trabeculae. (Modic *et al.* 1988a)

Besides differentiating the signal intensity changes Modic *et al.* also performed histologic studies of the endplate changes. These histologic studies showed disruption and fissuring of the endplates in type 1 MC. These endplates also showed regions of degeneration and regeneration and vascular granulation tissue. The marrow adjacent to the abnormal endplates show increased vascularity and edema possibly due to an inflammatory process. (Karchevsky *et al.* 2005, Modic *et al.* 1988a, Gendron *et al.* 2012)

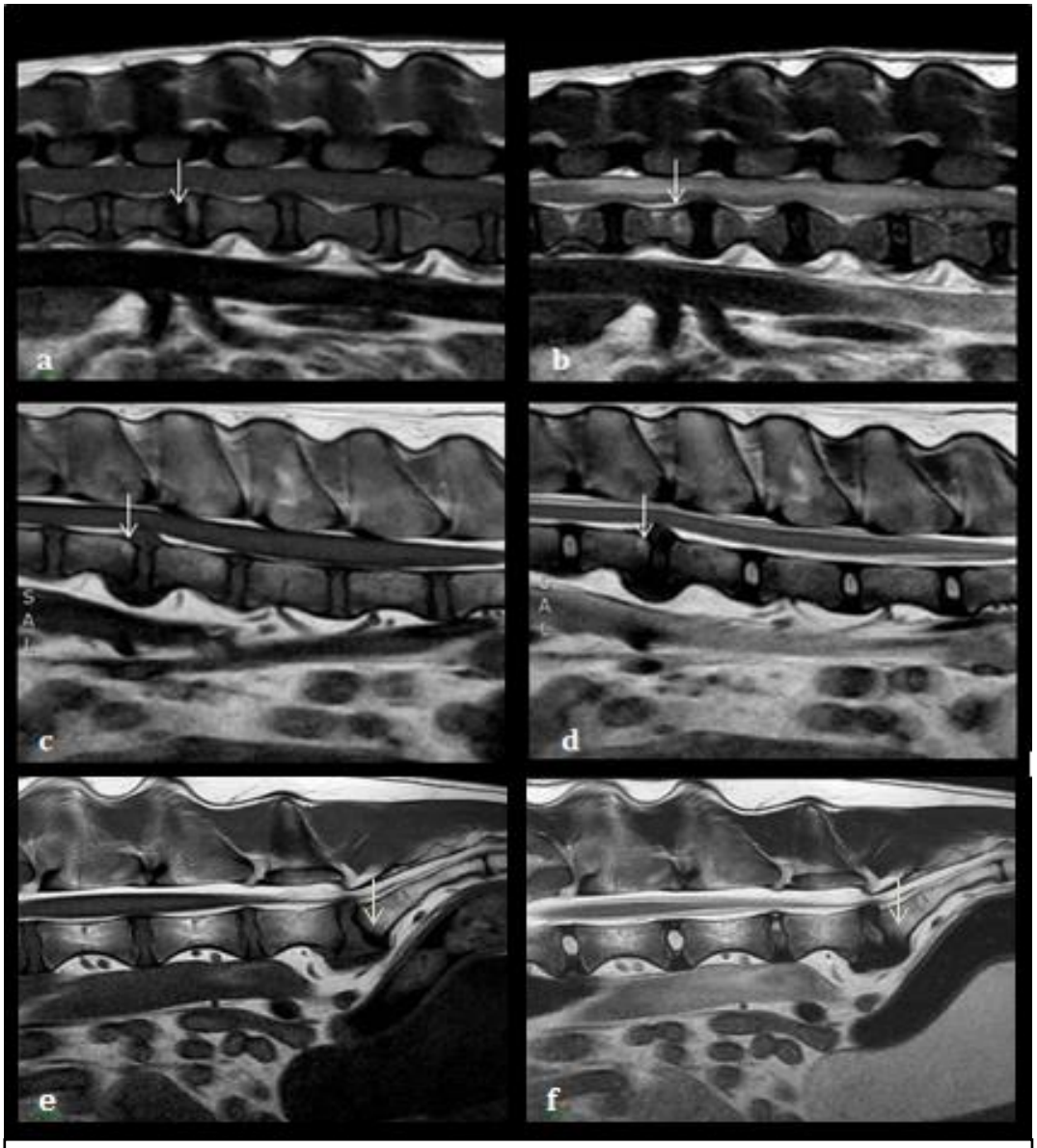


**Figure 1** Sagittal MR images showing MC type 1 on cranial (arrow) and a small change on the caudal endplate of L1-L2 on T1 Weighted image (a) and T2W (b). MC type 2 (arrow) on cranial endplate of L2-L3 on T1W (c)and T2W (d). MC type 3 (arrow) on caudal endplate of L7-S1 on T1W (e) and T2W (f).

The type 2 Modic changes demonstrated disruption of the endplate with distinct signs of chronic trauma (build-up of reactive bone and granulation tissue). The marrow adjacent to the abnormal endplate was lacking hematopoietic cells and was completely replaced by fat cells (yellow marrow), possibly due to marrow ischemia. (Karchevsky *et al.* 2005, Modic *et al.* 1988a). More elaborate research of the histologic differences of Modic changes has been performed by Perilli *et al.* in 2015. This research states that type 1 Modic changes have the highest bone turnover of the three types most likely caused by an inflammatory process. The type 2 Modic changes showed a reduced bone formation compared to type 1. Type 3 Modic changes showed increased bone formation and therefore an increase in bone volume and thickening of trabeculae (sclerosis). (Perilli *et al.* 2015)

These histological changes can explain the signal intensity changes on MRI. Type 3 Modic changes have low signal on T1W and T2W images due to the subchondral bone sclerosis and a decrease of marrow content and fat. Type 1 Modic changes have a low signal on T1W and high signal on T2W due to the edema.

*The cause of Modic changes*

About the pathophysiology of Modic changes there are multiple theories. One is that Modic changes are a result of mechanical stress at the vertebral endplate. (Albert *et al.* 2008, Van Dieën *et al.* 1999, Schmid *et al.* 2004) This theory is based upon the fact that disk degeneration is also a consequence of improper stress upon the disc and disk degeneration and Modic changes are correlated within humans. (Albert *et al.* 2007, Jensen *et al.* 2010) This overload of pressure on the vertebral disc can lead to an inflammatory reaction and micro-fractures and possibly cause the formation of Modic changes. (Kjaer *et al.* 2006, Albert *et al.* 2007)

The other theory is based on the process of infection. This theory suggests that an infection can cause the edema that gives the signal intensity changes in de vertebral endplate. These changes result from a pyogenic infection of the disc and adjacent endplates. As result of a tear in the outer annulus of the intervertebral disc, as in a herniation, an inflammatory reaction around the extruded disk material will occur. This environment of inflammation makes it possible for anaerobic bacteria to enter the herniated disk and cause a low virulent infection, which causes the Modic changes. (Albert *et al.* 2007) However, there are also some

studies performed that contradict this theory. A study performed by Wedderkopp *et al.* in 2009 showed no evidence of bacteria in endplates with Modic changes type 1.

*Pain and Modic changes*

In humans, Modic changes are correlated with nonspecific back pain. (Määttä *et al.* 2015) Especially type 1 Modic changes are strongly associated with lower back pain in humans. (Järvinen et al 2015, Kuisma *et al.* 2015, Bailly *et al.* 2014) A study performed by Albert *et al.* reported a prevalence of Modic changes of 18-58% amongst humans with lower back pain. (Albert *et al.* 2007) Jensen *et al.* found a similar result with a median prevalence of 43% in humans with clinical signs of lower back pain and a median prevalence of 6% in humans without clinical signs. (Jensen *et al.* 2008)

Modic changes have a strong relation with degenerative disc disease in the human spine. Degenerative discs however only show a slight correlation with lower back pain. Modic changes on the other hand have a strong association with lower back pain. (Kjaer *et al.* 2006) Why these Modic changes can cause pain in human patients has been investigated by Ohtori *et al.* This study showed that there is an increased expression of tumor necrosis factor (TNF) in the vertebral endplates of humans with type 1 and type 2 Modic changes in comparison to human patients with normal endplates on MRI. TNF and other pro-inflammatory cytokines are important factors for inflammation. This inflammatory response in the endplate affects the sensory nerves and could therefore cause pain. The same research showed that endplates with Modic type 1 or type 2 changes have an increased amount of nerve fibers. The ingrowth of nerves is possibly caused by the higher expression of TNF in these endplates. The higher expression of TNF and the ingrowth of nerve fibers in these endplates with Modic changes can explain that pain originates from these abnormal endplates. (Ohtori *et al.* 2006) Modic changes type 1 are most associated with pain because this type is associated with an early stage of inflammation, with many active inflammatory signs as earlier described. (Albert *et al.* 2007)

*Modic changes as a prognostic factor*

Studies have been performed to investigate the relation between Modic changes and disk degeneration and herniation. Shan *et al.* 2014 showed that spontaneous resorption of a disk herniation is less likely to occur when the patient is also showing Modic changes at MR imaging. This suggests that the presence of Modic changes on MRI could serve as a prognostic indicator for a possible therapy. More research has been performed to identify this potential prognostic ability of Modic changes. These studies have various outcomes. Jensen *et al.* 2011 is one of the studies that showed treatment outcomes are less favorable when Modic changes are present. Studies by Peterson *et al.* 2014 and Bensler *et al.* 2015 support this negative prognostic outcome when Modic changes are present. Another study also endorses this theory but showed a difference between the spinal location where the Modic changes are present. Modic changes in the lumbar area have a negative prognostic value, while on the contrary cervical Modic changes seem to have a positive prognostic value. (Kressig *et al.* 2016, Annen *et al.* 2016) Research also showed a difference in treatment outcomes between the different types of Modic changes. Modic changes type 1 have slow to no pain reduction within time in comparison to people with Modic changes type 2 or no Modic changes at all. (Jensen *et al.* 2011)

*Modic changes in the canine spine*

Research by Gendron *et al.* in 2012 showed that the same signal intensity changes as described in humans are also present within the canine spine. The spine of the dog is very similar to those of humans. It consists of 7 cervical vertebrae, 13 thoracic vertebrae, 7 lumbar vertebrae, 3 fused sacral vertebrae and a varying number of caudal vertebrae. (Evans *et al.* 2013) Between the vertebrae there is an intervertebral disc almost identical to the one in humans. Dogs are therefore often used as animal models for the process and therapy of disc diseases in humans. (Alini *et al.* 2008) This intervertebral disc functions as a shock absorber. This disc has three different components; the cartilaginous part of the vertebral end-plate, the annulus fibrosus and the nucleus pulposus. (Modic *et al.* 1988b, Evans *et al.* 2013, Brisson 2010)

This study by Gendron *et al.* also showed that Modic changes occur in the canine spine with a prevalence of 0.008 with a predilection site for the lumbosacral joint. Research methods used in this research are very different than those of the current study. Gendron *et al.* only used the dogs where was mentioned in the clinical report that Modic changes were present on MRI. They did not re-evaluate the MR images. Gendron *et al*. showed that in dogs there seems to be a predilection site for Modic changes; the lumbosacral joint and that MC2 was the most common change in the canine spine followed by MC1. (Gendron *et al*. 2012)

**Purpose of the study**

Nowadays many dogs are presented to their veterinarian with signs of lower back pain or vague complaints of discomfort originating from the lower back region. Since Modic changes are so strongly associated with lower back pain in humans it is possible that this is also the case in dogs. This means that the presence of Modic changes might be of clinical relevance in the work up of patients with lower back pain. This study aims on inquiring more information about Modic changes within the canine spine. The main question of this research is whether there is a correlation between the presence of Modic changes in the canine lumbar spine and clinical signs of lower back pain. Besides this main question associations between Modic changes, pain and other multifactorial variables, like intervertebral disc degeneration and herniation, will be investigated.

**Material and Methods**

*Study population*

The population for this study was selected from patients that were referred (from internal or external clinicians) for MR imaging of the lumbar spine during December 2013 to November 2016 to the Diagnostic Imaging Division of the Department of Clinical Sciences of Companion Animals, Utrecht University. Dogs were included when the MRI scan included sagittal T1- and T2-weighted images and when the imaged area included the lumbosacral junction. Dogs with fractures or neoplasia of the vertebrae were excluded from the study. Dogs with specific back problems like herniation of any grade, discospondylitis and/or degenerative discs disease were not excluded for this research, since literature suggests a relation between these diseases and Modic changes. (Peterson *et al.* 2014, Albert *et al.* 2013)

The age of all the dogs is notated in rounded years (continuous scale) but the dogs were also arranged in age classes; from pup (0 years old), adolescence (1-2 years old), adult (3-7 years old) and senior (>8 years). Same is performed for the weight of the dogs. Kilograms of the dogs are notated with one decimal (continuous scale) but also an arrangement is made in weight classes; small dogs (<10kg), medium dogs (10-25kg), large dogs (25-50kg) and giant dogs (>50kg).
Record is kept of what breeds the dogs are or if they were mongrels. The breeds are divided in chondrodystrophic breeds, non-chondrodystrophic breeds or unknown status of chondrodystrophy (in case of mongrels). The following breeds in the population were considered chondrodystrophic breeds: Basset Hound, Beagle, Cavalier King Charles Spaniel, (miniature) Dachshund, French and English bulldog, Pekingese, Shi Tzu, Tibetan spaniel, Toy Poodle, Pug and the Welsh Corgi. (Smolders *et al.* 2013, Bray *et al.* 1998)

*MRI technique*
The MRI studies were performed with a Philips Ingenia 1.5 T MRI. Standard spine imaging protocols were available for dogs weighing 10kg or 30kg.
The protocol for dogs of 10kg has imaging parameters of TR: 3000 and TE: 110 for T2-weighted imaging and TR: 400 and TE: 8 for T1 weighted images. The protocol for dogs of 30kg has parameters of TR: 2500 and TE: 110 for T2 weighted images and TR: 400 and TE: 8 for T1 weighted images. Dogs with weight greatly deviating from the standardized protocols were imaged with self-set parameters based upon the protocols.
After baseline imaging the imaging parameters were altered in some individual cases for better visualization of the abnormalities found on the MRI.

*Image assessment*
The sagittal T1- and T2-weighted images of the lumbar and lumbosacral spine were all evaluated by the same board certified veterinary radiologist. A more detailed explanation of the image assessment is included in Appendix A. Briefly; the MR images were evaluated on the following components:

1. The presence of Modic changes. The presence of signal intensity changes in the vertebral endplates was evaluated. Signal changes involving only a small region of the anterior corner of the vertebral body without extending to the majority of the end plate were not included in this study.
2. Type of Modic changes. The signal intensity changes were classified in accordance with Modic *et al.* 1988a, 1988b.
3. Severity of Modic changes. Each type of signal intensity change was individually scored for severity. When multiple types of Modic changes were present in the same endplate they were separately scored for severity. The scoring for severity was performed as described in the scorings sheet in Appendix A.
4. Location of the Modic changes. The location where the Modic changes are present was determined. First whether the Modic changes were present in the cranial and/or caudal endplate. Then the exact location per endplate was further scored as described in Appendix A.
5. Pfirrmann Grade. The Pfirrmann classification system is designed for grading lumbar intervertebral disc degeneration in humans. Research by Bergknut *et al.* 2011 revealed that this classification system is also applicable to canine intervertebral disc degeneration. The Pfirrmann grading system is focused on changes in the structure and signal intensity of the intervertebral disc on MR images and is described in Appendix A. (Pfirrmann *et al.* 2001)
6. Disc displacement. Displacement of the intervertebral disc included disc protrusion and disc extrusion. The amount of displacement is scored in accordance with the scoring system as described in Appendix A.
7. Discospondylitis. The MR images are subjectively evaluated for the presence of discospondylitis. The criteria for the diagnosis of discospondylitis are according to the imaging characteristics described by Gendron *et al.* 2012. (Appendix A)

*Disc degeneration*
After the image assessment a total disc degeneration score (DDD) will be calculated for all the dogs in the population individually. This DDD is made by summing up all the Pfirrmann grades from the IVD's from segment L4 to S1. Only these 4 segments will be used for the DDD since these segments are available on all the MR images of the dogs in this population. Besides, Modic changes are according to literature most located in the lower lumbar area. (Gendron *et al.* 2012, Zhang *et al.* 2008) The lowest possible score for the DDD is 4 and highest possible is 20.

*Retrospective pain analysis*
For this research it was necessary to evaluate whether animals were experiencing pain at the time of the MRI. Clinical records were retrospectively analyzed for signs of low back pain. A standardized scoring system was made to grade the clinical signs and localize the pain when present. This scoring system is made with non-specific signals of (back) pain that can be noticed by the owner and specific tests aimed upon diagnosing low back pain in the dog. For this scorings system 7 criteria were set up, for every criterion a dog meets, he is allocated a point. The specific physical tests for low back pain are of greater significance and are subdivided in grades of pain. Dogs with a total score of 2 or less were considered definitely not painful and total scores of 5 or higher were considered to be definitely painful in the lower back region. Animals with total scores of 3 or 4 points were assigned to the group of dogs were no conclusions could be made whether or not they were painful or not either due to vague clinical results or due to too little clinical information. The complete scoring system is described in Appendix B.

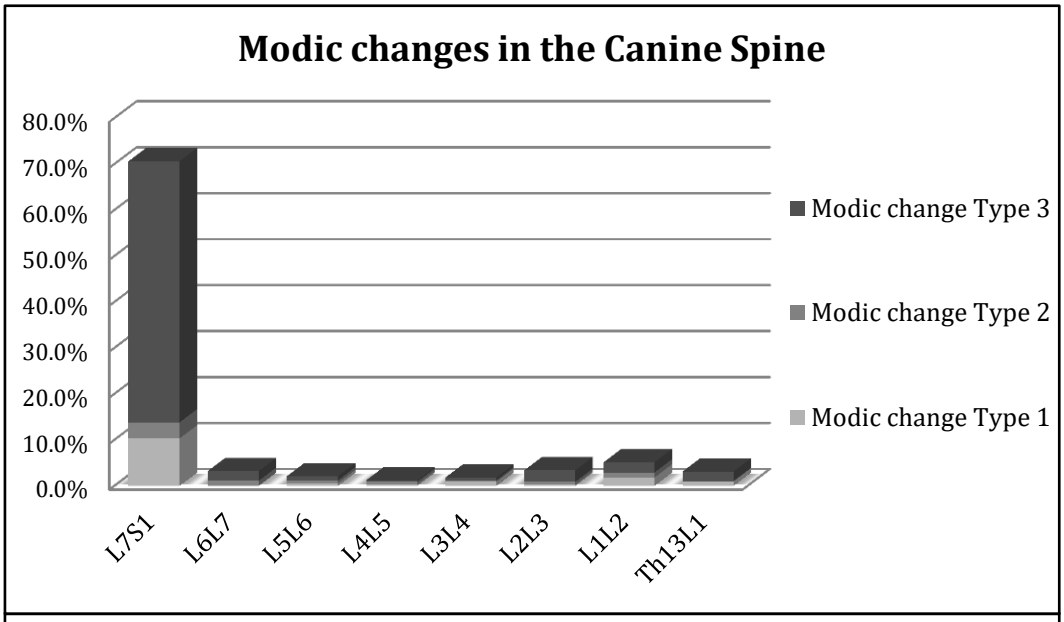


**Figure 2** Prevalence of the different types of Modic changes in percentages on the different lumbar intervertebral discs. A predilection site is seen on the L7-S1 segment compiled with a majority of Modic change type 3.

Besides analyzing the clinical history of the patients for signs of low back pain, the clinical records were also evaluated for mention of lumbar spine surgery prior to the MRI and this was notated. Other specific therapeutic treatments prior to the MRI like use of non-inflammatory drugs or antibiotics are not included in this research. Clinical records were also evaluated for results of bacterial cultures taken from the intervertebral disc after MRI was performed.

*Statistical analysis*

The retrieved information from this population was exported to IBM SPSS Statistics 24.0 software for descriptive statistics and the statistical analysis. With descriptive statistics the prevalence of the different types of Modic changes in the canine spine will be examined as will their locations within the endplates. Relation between individual variables will be tested using a Pearson's Chi Squared Test or Fisher's Exact Test. With logistic regression analysis the data will be tested for correlations between all the different variables and odds ratios will be calculated. The results were considered to be statistically significant if $p = < 0.05$.

**Results**

*Study population*

In the beginning of this research 340 dogs were included for this research. These dogs represent over 93 breeds. 290 dogs were purebred and 50 dogs were mongrels. The most represented breeds were the Labrador retriever (n=24), German Shepherd Dog (n=20), French bulldog (n=21) and the Dachshund (n=17). These breeds correspond to the most popular breeds in the Netherlands and our population is therefor similar to the rest of the Netherlands. (Den Bosch, H. A. S. 2015) 61 dogs of the study population were one of the previously described chondrodystrophic breeds, this means that 18% of the population is chondrodystrophic.

The dogs in the population have an average weight of 25,7kg (±15kg) ranging from 2,5kg to 88kg. Arranging the dogs in weight classes gives 60 small dogs (<10kg), 104 medium dogs (10-25kg), 155 large dogs (25-50kg) and 19 giant dogs (>50kg). From 2 dogs the weight was unknown.

The mean age of the dogs was 5,6 years (±2.9 years) ranging from 4 months to 15 years of age. Arranging the dogs in age classes leads to 9 pups (0 years old), 48 adolescent dogs (1-2 years old), 195 adults (3-7 years old) and 88 senior dogs (>8 years).

When comparing the weight and age of the chondrodystrophic (CD) and non-chondrodystrophic (NCD) breeds, it seems the NCD dogs are significantly older than the CD group with an average of 5.8 years for the NCD breeds and 5.1 years for the CD breeds (Fisher's Exact Test, P=0.003). Besides age, the NCD breeds are clearly heavier than the CD breeds with an average weight of almost 30kg in comparison to the average of 13kg of the CD group (Fisher's Exact Test, $p<0.001$)

154 of the dogs in this population were female from which 111 are castrated (72%). 186 of the dogs were male from which 87 are castrated (47%). The percentage of animals castrated is significantly different between the groups (Pearson's Chi Squared Test, $p<0.001$).

*Presence of Modic changes*

260 of the 340 dogs in this study showed signs of Modic changes in the lumbar region; this is nearly 77% of the population. Single Modic change types can occur, but also mixed types occur. 5 dogs had different types of Modic changes divided over multiple intervertebral disks in the lumbar spine while 49 dogs had different kinds of Modic changes in the same intervertebral disc.

The amount of intervertebral discs affected by Modic changes differs amongst the dogs. 227 of the dogs only showed Modic changes in one single intervertebral segment, 24 animals showed Modic changes in two different segments and only 9 animals showed Modic changes in three or more segments.

Figure 2 shows the distribution of Modic changes on the different lumbar segments with higher amount of Modic changes in the lumbosacral junction. Statistical comparison was performed to show that the lumbosacral junction of the canine spine is a predilection site for the presence of Modic changes. Pearson's Chi Squared Test shows that the amount of Modic changes on L7-S1 is significantly higher ($p<0.001$)

than in all the other lumbar intervertebral discs. 71% of the dogs in our population showed Modic changes in the lumbosacral junction. Only 6% of the dogs showed Modic changes in other IVD's than the LS junction.
Since there is a clear predilection site and there is a lack of numbers in the other IVD's the following of this research will be aimed on the changes around the intervertebral disc between L7-S1. For further analysis of the different types of Modic changes the mixed types are to be prioritized. Meaning that only one diagnosis was applied to the LS junction; type 1 Modic changes have the highest priority since there is a clear clinical relevance described in the human literature, followed by Modic change type 2 and last Modic change type 3, which is considered the least active type and is of least clinical relevance in the human literature. After this prioritization a clear majority of the Modic changes on L7-S1 is compiled by Modic change type 3 (figure 2). A few dogs (n=34) were diagnosed with Modic change type 3 but the severity of the changes was so low that for the following statistics these changes were considered to be irrelevant and therefore subsumed with the animals without Modic changes. After this the distribution of Modic changes on the L7-S1 segment is build-up with 159 dogs (77.2%) showing type 3 changes. Only 5.8% of the dogs showed Modic changes type 2 and 17% showed type 1 changes.
Taking a closer look at the localization of the Modic changes at the L7-S1 segment shows us that the majority of the Modic changes were located on the cranial vertebral endplate of the sacrum (75%). In 43% of these animals the Modic changes were located primarily at the ventral aspect of the endplate. In 28% of the cases the Modic changes were primarily located centrally and in 28% primarily at the dorsal aspect. 11% of the animals with Modic changes of the sacrum showed an asymmetry in the location of the Modic changes, a slightly higher percentage of the Modic changes have an asymmetry to the right side of the endplate.
No difference was found in the presence of Modic changes on the lumbosacral junction between males or females (Pearson's Chi Squared Test, p=0.330). Comparing the presence of Modic changes in CD and NCD breeds shows that NCD breeds and CD breeds have similar prevalence of Modic changes on the LS junction. (Pearson's Chi Squared test, p=0.348).

Results show that the presence of Modic changes increase in time (Figure 3). A significant difference is noted between the presence of Modic changes and the different age classes (Fisher's Exact Test, p=0.001) Another significant difference is found between the presence of Modic changes and body weight (Pearson's Chi Squared Test, p<0.001). The individual relation between disc degeneration and Modic changes are also significant (Pearson's Chi-Squared Test, p<0.001).

Logistic regression is used as statistical analysis to find out whether there are predictors for the presence of Modic changes. The logistic regression is focused on the presence of Modic changes on the lumbosacral junction with explanatory variables as gender, breed (CD or NCD), age, weight, disc degeneration and disc protrusion. Results are that the protrusion of the IVD of segment L7-S1 is an independent predictor for the presence of Modic changes at the adjacent endplates. The different protrusion scores were compared to animals without any signs of protrusion.

| | *B* | *SE* | *Wald* | *Df* | *Sig.* | *Exp(B)* | *95%CI for EXP(B)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | lower | upper |
| **<25% protrusion** | **0.890** | **.305** | **8.500** | **1** | **.004** | **2.436** | **1.339** | **4.433** |
| **>25%<50% protrusion** | **1.284** | **.352** | **13.342** | **1** | **.000** | **3.611** | **1.813** | **7.192** |
| **>50% protrusion** | **2.689** | **.515** | **27.281** | **1** | **.000** | **14.711** | **5.364** | **40.344** |
| **Extrusion** | **2.839** | **.769** | **13.625** | **1** | **.000** | **17.105** | **3.788** | **77.249** |

**Table 1** This table shows the odds ratio's (ExpB) and the confidence intervals of the IVD protrusion scores as a positive predictor for the presence of Modic changes on L7-S1.

All the grades of disc protrusion are significantly related to the presence of Modic changes (Table 1).
To summarize, statistical analysis shows that there are individual relations between the presence of Modic changes and weight, age, disc degeneration and disc protrusion. When performing a logistic regression analysis only disc protrusion comes out as a significant risk factor for the presence of Modic changes on the lumbosacral junction.
However, since there is multicollinearity between the variables age, weight, disc degeneration and disc protrusion. Analyzing which of these factors is the strongest predictor for Modic changes is difficult and thus yet undetermined.

To compare our canine population with the human population a separate regression is performed which only included the non-chondrodystrophic dogs, since the intervertebral discs of these dogs resemble the human discs the most**.** (Alini *et al.* 2008) Logistic regression analysis was yet again used for the development of Modic changes in the lumbosacral-junction for NCD breeds. A significant association was found between protrusion score and the presence of MC in NCD breeds. <25% protrusion has an odds ratio of 2.230 (95% CI 1.132-4.390, p=0.020), >25%-<50% protrusion has an odds ratio of 3.505 (95% CI 1.619-7.589, p=0.001) >50% protrusion has an odds ratio of 14.375 (95% CI 4.615-44.774, p<0.001) and extrusion has an odds ratio of 27.929 (95% CI 3.521-221,502 p=0.002). The same analysis for CD breeds gives positive associations between Modic changes and weight (kg) (OR: 1.116, 95% CI 1.012-1.231, p=0.028) and protrusion of more than 50% vertebral canal stenosis (OR: 15.930 [95% CI 1.682-150.857, p=0.016]).

*Correlation between clinical signs and Modic changes*
While analyzing the clinical records of the dogs it showed that all dogs were referred with a clinical indication of back problems. The reasons for referral of these patients for MRI were clinical signs differing from low back pain to paresis/paralysis and others, but all were suspected of spinal problems. 20,6% of the animals showed paresis and 8,5% showed paralysis before undergoing the MRI. In 10,3% of the animals the neurological status was unknown due to too little clinical information.
From the 340 dogs included in this research 12 were excluded for the pain analysis since there were other pathologies present like intra- or extradural malignancies. 36 dogs were excluded for the pain analysis due to lack of clinical history available to confidently determine whether they were suffering from low back pain. The pain analysis is performed with 292 dogs. The 292 dogs for this study were assigned in groups according to the pain scorings sheet as described in Appendix B: not painful (n=64), doubtful pain (n=52) and definitely painful (n=176).

In view of the logistic regressive analysis the group of animals with doubtful pain is redistributed. The results of the specific physical tests for lumbar pain were the decisive factors for making the decision whether or not the dogs were painful. This resulted in two groups: painful (n=198) and not painful (n=94). Individual correlation tests with Pearson's Chi Squared Test showed no significance between pain and protrusion scores on L7-S1 (p=0.481), between pain and disc degeneration on L7-S1 (p=0.460) and between pain and the presence of Modic changes on L7-S1 (p=0.087). When performing a logistic regression analysis for the possible explanatory variables of low back pain. The tested explanatory variables are all not significantly correlated to the presence of low back pain.

*Disc degeneration*

This population has a median disc degeneration score (DDD) of 9, measured over lumbar segments L4-S1. Comparing the DDD score between the CD and NCD group shows that the CD breeds have higher DDD scores (Pearson's Chi Squared Test, p<0.001). Median DDD of the NCD group is 9 in comparison to the DDD of 13 of the CD group. When comparing the DDD of the CD and NCD breeds in relation to age reveals that CD breeds have higher total DDD at a younger age than NCD breeds and remain at a higher level throughout their lives (Figure 4). A decrease is visible in the disc degeneration score of the CD breeds at age 2, but only two dogs represent this age. Taking a closer look at the degeneration scores of segment L7-S1 specifically shows again that CD breeds have higher disc degeneration at this site. 80% of the CD breeds have a degeneration score higher than Pfirrmann grade 3, of the NCD breeds 53.3% have Pfirrmann grade 3 or higher on the LS junction. Age and disc degeneration are significantly correlated with each other (Fisher's Exact Test, p<0.001). Weight is not correlated with disc degeneration on L7-S1 in this population (p=0.914).

Associations between the presence of disc degeneration on L7-S1 and the variables gender, age, weight, breed (CD or NCD), protrusion scores and types of Modic changes also showed some significant numbers. An animal was considered to have disc degeneration when they showed Pfirrmann grades of 3 and higher. In this equation gender also does not seem to be of impact. Age shows an odds ratio of 1.323 (95% CI 1.192-1.468, p<0.001) for every year an animal gets older. Chondrodystrophic breeds have 6.052 (95% CI 2.888-12.686, p<0.001) more chance of getting disc degeneration in comparison to non-chondrodystrophic breeds. Especially the dogs with protrusion scores of >50% vertebral canal stenosis show increased chance of having disc degeneration with an odds ratio of 7.366 (95% CI 2.828-19.184, p<0.001) in comparison to dogs without protrusion. Modic changes type 1 are also positively associated with disc degeneration on L7-S1 with an odds ratio of 9.856 (95% CI 1.956-49.659, p=0.006).

*Disc protrusion*

40.3% of the study population has protrusion on the LS junction larger than 25% of vertebral canal stenosis. Between weight of the dog and the presence of disc protrusion >25% is a significant correlation (Pearson's Chi Squared Test, p<0.001). Comparing the different age groups and the protrusion scores there is a significant correlation between age and protrusion of the disc

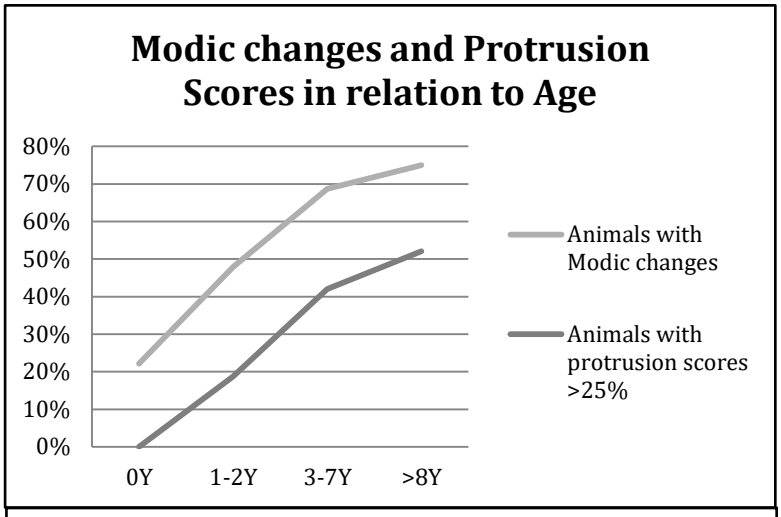


**Figure 3** This graph shows a clear increase in the amount of animals showing Modic changes on LS-junction when getting older (light grey line). In the same graph is visible that the amount of animals with protrusion scores of >25% of vertebral canal stenosis or extrusion of the disc on LS- junction increases when animals getting in older age classes (dark grey line).

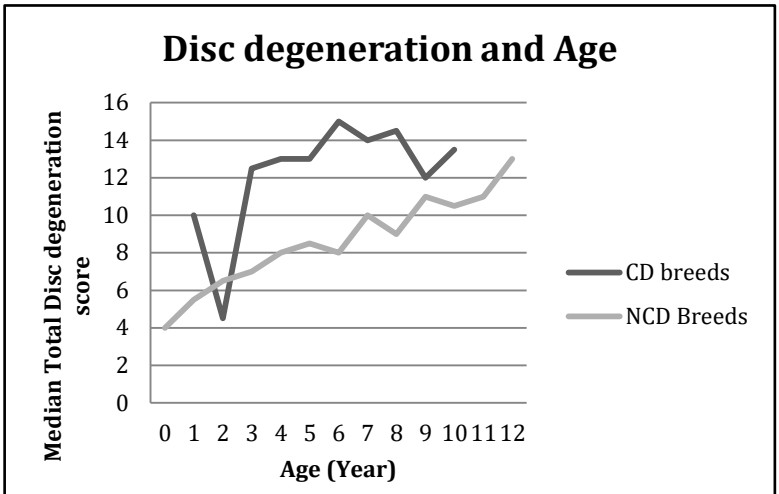


**Figure 4** This graph shows the difference in disc degeneration between chondrodystrophic (CD) breeds (dark grey) and non-chondrodystrophic (NCD) breeds in relation to age. Disc degeneration increases in time, with higher degeneration in CD breeds.

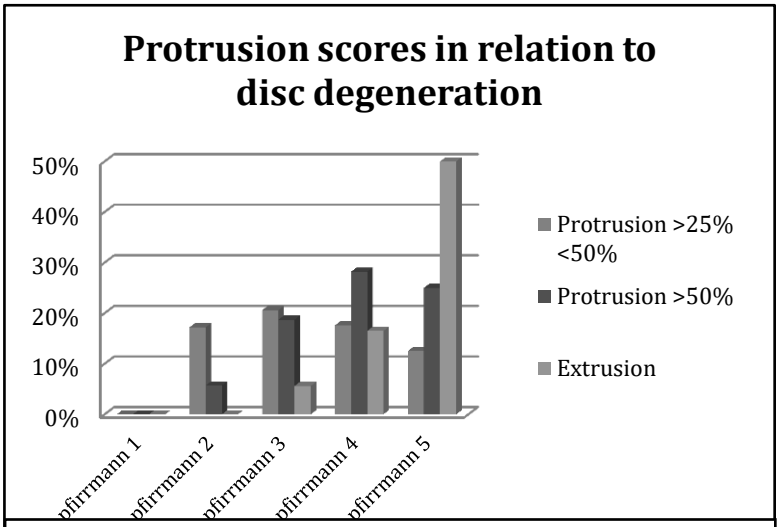


**Figure 5** This chart shows the increase of dogs with protrusion score >25% of vertebral canal stenosis or extrusion of the disc in relation to disc degeneration expressed in Pfirrmann grades on L7-S1.

(Fisher's Exact Test, p<0.001) (Figure 3). As visible in figure 3 the presence of Modic changes and the presence of disc protrusion >25% both increase simultaneously when animals get older. The association between Modic changes and disc protrusion is already significantly tested in the paragraph above. But Modic changes and protrusion individually also have significant correlations with age as visible in figure 3. When comparing the Pfirrmann grades of L7-S1 and the corresponding protrusion scores it shows that dogs with more than 25% disc protrusion and/or extrusion have higher degeneration scores (Figure 5). This relation between disc degeneration and disc protrusion is significant (Pearson's Chi Squared Test, p<0.001). When comparing the protrusion scores of L7-S1 amongst CD and NCD breeds it shows that 42.7% of the NCD breeds have protrusion larger than 25% in comparison to 33.8% of the CD breeds, but this difference is not significant (Pearson's Chi Squared Test, p=0.197). Performing logistic regression analysis for the presence of protrusion >25% at L7-S1 shows a positive association with Modic changes (OR: 4.040, 95% CI 2.339-6.978, p<0.001), age in years (OR: 1.157, 95% CI 2.057-1.266, p=0.002), weight in kg (OR: 1.028, 95% CI 1.011-1.046, p=0.001).

*Discospondylitis*

21 animals in this population showed signs of discospondylitis on MR imaging, this is 6% of the population. All dogs with signs of discospondylitis also showed Modic changes on MRI. In 29 animals interdiscal swabs were taken during a surgery procedure after the MRI, and cultured for bacterial growth. In 11 dogs bacteria could be isolated out of the sample. Six dogs who showed signs of discospondylitis on MRI only one was cultured positive (17%). 10 dogs had positive swabs but showed no signs of discospondylitis on the previous MRI. 45% of the positive swabs showed coagulase-negative staphylococci. The other swabs consisted of other pathogens as *Streptococcus*, *Pasteurella Canis*, *Neisseria* spp., *Bacillus* spp. and a mixed culture.

In total 11 swabs came back positive, 6 of the dogs with the positive swabs showed Modic changes on MRI and all of these changes were type 3 endplate changes.

*Previous spinal surgery*

17 dogs had spinal surgery performed to the lumbar spine prior to the MRI, one dog even underwent 2 surgical procedures before the MRI. 82% of the operated segments showed Modic changes after surgery. 38.5% of the segments showed Modic changes type 3, 38.5% showed Mixed Modic changes type 1 and 3. After prioritizing the Modic changes it results in 6 segments with Modic changes type 1, 2 segments with Modic change type 2 and 6 segments with Modic change type 3. Comparing the amount of animals with Modic changes after surgery and without surgery no difference is found (Pearson's Chi Squared Test, p=0.549). When comparing the prioritized Modic changes there is a significant increase of Modic changes type 1 after surgery when compared to animals who did not undergo spinal surgery, odds ratio 3.61 (Fishers Exact Test, 95% CI 1.293-10.256, p=0.020)

## Discussion

*Modic changes*

Results from this study suggest that MC have a predilection for the lumbosacral junction and that disc protrusion is a risk factor for the formation of MC at this site. The prevalence of Modic changes found in our study population (0.77) is severely higher than the previously mentioned 0.008 in research performed by Gendron *et al.* in 2012. However a real comparison between these 2 studies is hardly relevant since very different methods are used. Where Gendron *et al*. only used dogs where Modic changes were mentioned in their MRI report, in this study all MRI studies were retrospectively analyzed with special attention to the presence of Modic changes. (Gendron *et al.* 2012) We can conclude from this study that Modic changes are much more common when special notice is being held at the presence of Modic changes on MRI. A shortcoming of this study is that all the animals were referred for imaging with a suspected problem in the back area. This means that our population is biased and for more reliable prevalence numbers a study has to be performed with an asymptomatic control group. The prevalence of MC in the human spine varies from 18 to 58% in patients with lower back problems and around 6% in an asymptomatic population. (Albert *et al*. 2007, Jensen *et al.* 2008) The distribution of MCs in the human spine is comparable to what was found in this study, because also in humans the lower part of the spine is most often affected (L4-L5-S1). (Zhang *et al.* 2008) Gendron's study also reported a predilection site for Modic changes on the lumbosacral junction in the dog. An explanation for the higher prevalence of Modic changes at this site is that the lumbosacral junction differs from other lumbar segments and is often called the lumbosacral joint, which already suggests a different motion pattern. This segment has more mobility in flexion and extension of the back than other lumbar segments and it also allows rotation and lateral bending. This increased mobility in the lumbosacral joint can cause repetitive stress and therefore predispose for disc degeneration at this site. Other congenital or genetic abnormalities can also predispose for disc degeneration at this site. (Meij *et al*. 2012) Disc degeneration is the factor strongest related to Modic changes in the human spine. (Arana *et al.* 2011) Therefore explaining the predilection site for the lumbosacral junction. The current study has similar results about the relation between disc degeneration and Modic changes, however it is not considered the strongest factor as in human medicine.

Further characteristics of the Modic changes in this study showed a slight predilection to the ventral part of the vertebral endplate of the sacrum. Human literature shows that in symptomatic patients the Modic changes are equally distributed over the cranial and caudal vertebral endplate. A predilection to the ventral part is, just like in this study, also mentioned in the human literature, but no explanation can be found for the clinical relevance of this finding. (Jensen *et al.* 2009, Zhang *et al.* 2008)

Modic change type 3 is most often seen in this canine population. This differs greatly from the previously performed study by Gendron *et al.* 2012 who reported that MC type 2 was most common. However, as previously mentioned, a comparison between these studies is hardly relevant. We can assume that Modic changes and especially Modic change type 3 is far more common than previously suspected. In human literature it is reported that type 1 and type 2 are the most common types. (Zhang *et al*. 2008) The difference between the human and canine population could be caused by anatomical differences, although specific literature comparing the anatomy and biomechanics of the two species are not available. Nevertheless it seems clear that humans and dogs have different forces upon their

vertebrae. Humans carry all their weight on their two legs, therefore a more vertical pressure will be applied on the endplates. Dogs have their weight divided over 4 limbs, which causes a very different spread of the forces over their spine. However this does not explain why MC3 is more common in the canine spine and more research needs to be performed to fully discover the possible cause. Another theory why type 3 endplate changes are more often seen within the canine population could be the more chronic stage in which the patients are presented. Since humans can easily express their discomfort originating from lower back pain, they are more likely to be imaged with MRI during a more acute and active state, reflected by a higher prevalence of Modic changes type 1 and 2. For dogs this is clearly different. Recognizing pain in dogs is difficult and back pain often expresses itself by very nonspecific signs. (Meij *et al.* 2012) It is speculated that before a dog is referred for MR imaging a relatively long time has passed, where multiple nonspecific pain reducing and anti-inflammatory drugs have been tried. However no special notice is held at the previously prescribed medication in this particular study, we may assume that many of the dogs received some form of pain reducing medication prior to the MRI since they were all referred with an indication of low back problems. The chances of capturing the more chronic phase (type 3 changes) when imaging a dog is therefore greater than in humans. This is however just a hypothesis and further research is necessary to further investigate this difference in prevalence.

Modic changes are mostly seen in humans with the age of 40-50 years old and a clear relation between age and Modic changes is reported. (Jensen *et al.* 2008) In this study a similar relation is seen between age and the presence of Modic changes in dogs (Figure 3). Another relation with the presence of Modic change mentioned in the human literature is weight, which is also seen in the current study. This can explain the possible pathogenesis of MC due to mechanical stress to the endplates that potentially leads to micro fractures. Since a higher weight increases the pressure on the endplates which gives more chance on the formation of micro-fractures and therefore Modic changes. (Kjaer *et al.* 2006, Albert *et al.* 2007) Research showed that not BMI is a risk factor but actual weight is. (Karchevsky *et al.* 2005) The average weight of the population used in this study is reasonably high (25.7kg). This can be explained by the fact that all these dogs used in the population are referred for MRI with clinical signs of back problems in the lumbar region and research shows that problems in the lumbosacral area are mainly seen in large breed dogs. (Meij *et al.* 2010, Smolders *et al.* 2013) A weakness of this current study is that no attention is paid to the relative age and weight differences in the different breeds. Since breeds have different weight and live expectancy's. Attention is paid to the difference of age and weight between the CD and NCD breeds. This study shows that in this population the NCD breeds are heavier than the CD breeds, this is explained by the fact that CD breeds tend to be smaller breeds than NCD breeds. (Smolders et al. 2013) The amount of females castrated in this population is also noticed. 72% of the female dogs are castrated in relation to 47% of the males. This difference is found significant ($p<0.001$) in this study. This high amount of castrated female dogs in the population can be explained by the fact that females are more often spayed due to medical and behavioral consequences which can occur in intact females and for owner convenience. (Kustritz *et al.* 2007)

However individual relations are found between Modic changes and various variables, only disc protrusion is considered an independent risk factor in this study after logistic regression analysis. However, since the multiple relationships between the different variables, so called multicollinearity, differentiating which of the variables is the strongest risk factor for the presence of Modic changes is not able from this study.

That Modic changes have a link to a couple of disc diseases is elaborately described in literature. For example within humans there is a strong association between degenerative disc diseases and disk herniation and the presence of Modic changes in the lumbar spine. (Mann *et al.* 2014, Kressig *et al.* 2016) There are multiple studies performed which investigate this correlation between intervertebral disc diseases and the presence of Modic changes in humans. Some studies show that humans with signs of disk degeneration are more likely to show Modic changes on MRI. (Albert *et al.* 2007, Jensen *et al.* 2010) Modic himself also found this relation between Modic changes and degenerative disc degeneration in the human spine. (Modic *et al.* 1988a) He noticed that the changes in signal intensity of the marrow are often seen in the vertebral bodies adjacent to intervertebral discs with degenerative changes or herniated intervertebral discs. Modic changes therefore seem to be strongly correlated with degenerative intervertebral disc diseases in the human spine. A study by Kerttula *et al.* 2012 even suggests that Modic changes type 1 are precursors of rapidly progressive disk degenerative disorders in humans. (Kerttula *et al.* 2012, Luoma *et al.* 2009) Logistic regression performed on data of this study also showed that Modic change type 1 is an independent risk factor of disc degeneration. This result supports the theory of Kerttula *et al.* that MC type 1 is more strongly related to degenerative disc disease than the other types of Modic changes.
That the presence of Modic changes increases when there is adjacent disc degeneration is also supported by the results of this study. Even though disc protrusion is considered the strongest factor for the presence of Modic changes in this study a relation between disc degeneration and disc herniation cannot be denied. (Smolders *et al*. 2013, Urban *et al*. 2003) Disc degeneration can cause disc herniation due to the degeneration of the annulus fibrosus and the nucleus pulposus. (Smolders *et al.* 2013) Disc degeneration is related to age since it is a progressive disease. In this study a difference is noticed between the chondrodystrophic and non-chondrodystrophic breeds in disc degeneration (Figure 4). The chondrodystrophic breeds have higher degeneration scores at a younger age and maintain having higher scores than NCD breeds. This corresponds to what is published. (Smolders *et al*. 2013) The degenerative process of the intervertebral disc has a slightly different course in the CD breeds. In CD breeds the degeneration occurs around 3-7 years and in NCD breeds later in life, around 6-8 years. From birth there is a difference noticed within the transitional area in-between the collagenous part of the annulus fibrosus (AF) and the nucleus pulposus (NP). In CD breeds this transition zone is broad, meaning the collagenous part of the AF is narrower, and the cells in this area lack orientation. In NCD breeds this transition area is more distinct. Disc

degeneration starts with degeneration of the NP, which is already noticed in CD breeds at an age of around 4 months. The notochordal cells in the NP are gradually replaced by chondrocyte-like cells; this process starts in the periphery of the nucleus and then spreads. These chondrocyte-like cells rapidly go into apoptosis, a process that progresses quickly with increasing age. In NCD breeds the degenerative process of the NP is largely similar, however in these breeds the notochordal cells remain the dominant cell type in the NP. This is different as in CD breeds where complete replacement of the cells is often seen. After the NP degeneration the AF starts degenerating, usually at one specific location, with replacement of the cells by chondrocyte-like cells and by separation of the lamellae in the annulus. In CD breeds this degenerative process is quickly progressive and can lead to herniation's with a sudden onset due to complete rupture of the AF and with extrusion of the disc as a consequence (Hansen type 1 herniation). In NCD breeds this process of degeneration often happens much more gradually which results in partial ruptures of the lamellae in the annulus leading to protrusions of the intervertebral disc (Hansen type 2 herniation). Even though Hansen type 1 is more common in CD breeds and Hansen type 2 in NCD breeds, they both occur in all breeds of dogs. (Smolders *et al*. 2013)

Results in this population showed that the protrusion scores from segment L7-S1 between CD breeds and NCD breeds were not significantly different, while disc degeneration of CD breeds is significantly higher. This can be related to the characteristics of the disc degeneration and herniation as described above. CD breeds are characterized by their rapid degeneration, hence the high degeneration scores. However the herniation within CD breeds is often a Hansen type 1, this means it has a sudden onset and often results in extrusion of the disc. Dogs in the NCD group generally have a more gradual onset of degeneration which leads to protrusion of the disc. The NCD breeds are often larger breed dogs and are predisposed for lumbosacral disc diseases, while the CD breeds show disc degeneration and herniation throughout their whole spine. (Smolders *et al*. 2013, Meij *et al.* 2010)

In human literature a relation is described between previous spinal surgical procedures and the presence of Modic changes. One year after spinal surgery the presence of Modic changes in humans is significantly higher, especially MC type 1. (Elbarzouhi *et al.* 2014) Within the current study population a similar relation is found between surgery and Modic changes. Research by Elbarzouhi shows that patients 1 year after surgery have an odds ratio of 8.6 to have an increase in the extent of Modic changes, especially in type 1 changes. The current study showed a significant increase of Modic changes type 1 when compared to the population which did not have surgery. Shortcoming of this comparison is that this study did not have MR images from before the surgery and a direct increase of Modic changes within the patients is therefore unknown. In addition, the number of dogs that were used for this analysis was very low (n=17).

Another finding of this study that needs to be addressed is the presence of positive culture swabs in dogs without the classical imaging characteristics of discospondylitis on MRI.
In human literature *Staphylococcus aureus* is the most common pathogen found in patients with discospondylitis. But a broad spectrum of pathogens can be found such as coagulase negative staphylococci, streptococci, or even fungi. The pathogens can cause infection in the spine through haematogenous spread or after spinal surgery. (Gouliouris *et al.* 2010) Human literature describes that in 30-50% conventional disc culture techniques fail to diagnose the pathogen, and DNA-based methods are now more frequently used in human medicine. (Lecouvet *et al.* 2004) In our study population only 17% of the swabs, taken from dogs with signs of discospondylitis on MRI, diagnosed a pathogen. 10 dogs positively cultured in this study did not have signs of discospondylitis on MRI. To the authors knowledge, this has not been reported in dogs before. The samples were taken during surgery under strict sterile conditions and therefore contamination is unlikely. Besides, with contamination multiple bacteria are often cultured. This was not the case with exception of one case where a mixed culture with two bacteria was found. All the dogs from which bacterial cultures were taken had surgery due to disc herniation. In human research by Albert *et al*. in 2013 they also performed bacterial cultures of the discs of patients during surgery due to herniation. They found that 46% of the patients had positive bacterial cultures, the majority was anaerobic. Within our study population 29 dogs that went for surgery due to herniation were cultured and from these dogs 11 were cultured positively (40%). This is very similar to the results from the study by Albert *et al.* 2013. They suggest the explanation that when a herniation has occurred low virulent anaerobic bacteria can enter the disc. Due to the low vascularization in the disc an anaerobic environment exists, ideal for the anaerobic bacteria to develop. Most likely the same theory is applicable to the positive cultures in our study population. Albert *et al.* also described that mainly MC1 are present when anaerobic bacterial cultures were found. Their explanation is that due to a reaction at the low virulent infection in the disc, the adjacent endplates react by the formation of edema, seen as Modic changes type 1 on MRI. In addition to the theory Albert *et al.* found that the patients with MC1 significantly improved to antibiotic treatment on pain, function and MRI, which supports the possible influence of bacteria in the pathogenesis of Modic changes. (Albert *et al.* 2013) In our study 6 of the 11 positive tested dogs (55%) showed Modic changes on MRI. All of these changes were type 3 endplate changes. Thus, the described relation between Modic changes type 1 and anaerobic bacteria is not seen in our population. Within human studies this relation is also still not fully discovered and further research is obligated to test this theory. (Wedderkopp *et al*. 2009)

In this study no relation is found between lower back pain in the dog and the presence of Modic changes, while this relation is often described within human research. (Albert et al. 2013, Määttä *et al.* 2015, Järvinen *et al.* 2015) However there are serious limitations to this study when drawing conclusions regarding pain. Determining pain in animals is difficult and retrospectively deciding if a dog is painful on the basis of clinical reports written by different clinicians is even harder. To fully discover the possible relation between Modic changes and pain in dogs, new research needs to be performed with systematic physical examination, ideally performed by a single veterinary orthopedic specialist. But even with these specialized circumstances a relation will be difficult to establish. In the human literature they established the relation between Modic changes and lower back pain by aid of questionnaires and discography with mixed results.

(Albert *et al*. 2008, Weishaupt *et al.* 2001, Braithwaite *et al.* 1998) Another shortcoming of the current study is that no difference is made between the different types of endplate changes and low back pain, since the high prevalence of MC3 in relation to the other types makes statistical testing insignificant.

Besides not finding a relation between MC and pain, our study population neither showed relations between pain and disc degeneration and herniation. Lower back diseases in veterinary medicine are known for their non-specific clinical signs and our results support that. Research by Penning *et al*. supports the theory that no clear associations can be made between the amount of protrusion of a herniated disc and clinical signs. (Penning *et al*. 2006) Some studies performed with human patients also raised questions about the relation between MRI findings of protrusion and disc space narrowing and the presence of lower back pain. (Stadnik *et al*. 1998, Videman *et al*. 2003)

**Conclusions**

Modic changes types 3 are a common finding on MR images of dogs, scanned with an indication of back problems. Modic changes in the dogs have the highest prevalence on the L7-S1 segment. In this study a significant association is found between the extent of protrusion and extrusion of the intervertebral disc of L7-S1 and the presence of Modic changes as an independent variable.
No relation has been found between the low back pain and the presence of other radiographic findings.
Disc degeneration is positively associated with age, chondrodystrophia, disc protrusion and Modic changes type 1.

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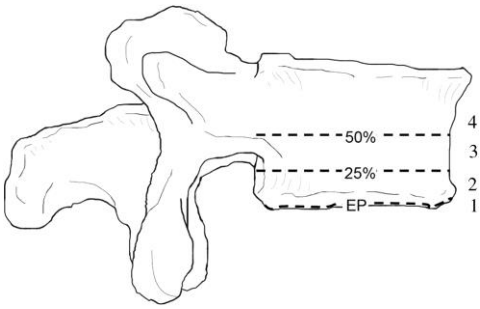
## Appendix A

1. <u>The presence of Modic changes.</u>
   The presence of signal intensity changes in the vertebral endplate is evaluated. Signal changes involving only a small region of the anterior corner of the vertebral body without extending to the majority of the end plate were not included in this study.

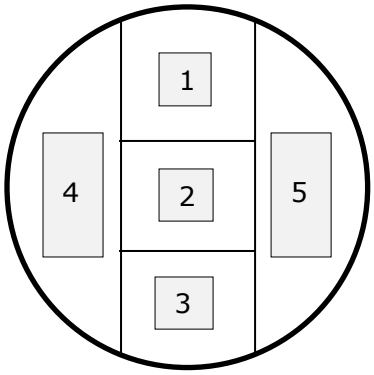
2. <u>Type of Modic changes.</u>
   The signal intensity changes are classified in accordance with Modic *et al.* 1988a, 1988b:
   - Type 1 Modic changes are characterized by decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images.
   - Type 2 Modic changes have increased intensity in T1-weighted images and have the same or a slight increase in intensity on T2-weighted images.
   - Type 3 Modic changes are marked by decreased signal intensity on T1- and T2-weighted images.

3. <u>Severity of Modic changes</u>.
   Each type of signal intensity changes is individually scored for severity. So when there are multiple types of Modic changes in the same endplate they will be separately scored for severity.




   a. <u>Grade 0</u>: the endplate shows no abnormalities or signal intensity changes
   b. <u>Grade 1</u>: doubtful, the endplate shows no distinct abnormalities but has a signal intensity change that does not exceed 10% of the vertebral height.
   c. <u>Grade 2</u>: mild, the signal intensity change is in-between 10 and 25% of the vertebral height.
   d. <u>Grade 3</u>: moderate, the signal intensity change is in-between 25 and 50% of the vertebral height.
   e. <u>Grade 4</u>: severe, the signal intensity change is equal to or more than 50% of the vertebral height.

4. <u>Location of the Modic changes.</u>
   The location where the Modic changes are present will be scored. First will be determined if the Modic changes are present in the cranial or caudal endplate. Then in a sagittal view of the MRI the Modic changes will be differentiated in location using codes.




   a. <u>1</u>: Dorsal location of the Modic changes.
   b. <u>2</u>: Central location of the Modic changes.
   c. <u>3</u>: Ventral location of the Modic changes.
   d. <u>4</u>: Asymmetrical location of the Modic changes to the right.
   e. <u>5</u>: Asymmetrical location of the Modic changes to the left.

   Locations 1, 2 and 3 can arise individually but also in combinations. Location 4 and 5 are only to indicate a asymmetry and to what side this asymmetry is located. These are always in combination with one (or multiple) of the first 3 locations.

5. Phirrmann Grade.
   The Pfirrmann classification system is designed for grading lumbar intervertebral disc degeneration in humans. Research by Bergknut *et al.* 2011 revealed that this classification system is also applicable to canine intervertebral disc degeneration. The Pfirrmann grading system is focused onchanges in the structure of the intervertebral disc. For this system four components are evaluated; Disc structure, T2-weighted signal intensity, distinction between the nucleus and annulus and disc height. (Pfirrmann *et al.* 2001)

| ***Pfirrmann grade*** | ***Structure*** | ***Distinction between nucleus and annulus*** | ***Signal intensity*** | ***Height of IVD*** |
|---|---|---|---|---|
| I | Homogeneous and bright white | Clear | Hyper-intense and isointense to CSF | Normal |
| II | Non-homogeneous with or without vertical bands | Clear | Hyper-intense and isointense to CSF | Normal |
| III | Non-homogeneous and grey | Unclear | Intermediate to CSF | Normal to slightly decreased |
| IV | Non-homogeneous and grey to black | Lost | Intermediate to hypo-intense to CSF | Normal to moderately decreased |
| V | Non-homogeneous and black | Lost | Hypo-intense to CSF | Collapsed disc space |

6. Disc displacement.
   Displacement of the intervertebral disc included disc bulge, disc protrusion and disc extrusion. Disc bulge was defined as a displacement of the disc beyond the line of the posterior edges of the adjacent vertebral bodies. Protrusion of the disc is when the nucleus is displaced beyond the borders of the annulus fibrosus. Extrusion of the intervertebral disc was defined as a nucleus displacement that extends above or below the disc level. The protrusion/extrusion is graded in accordance with the following system.
   a. Grade 0: No or subtle
   b. Grade 1: Clear but <25% of vertebral canal stenosis
   c. Grade 2: >25%, <50% of vertebral canal stenosis
   d. Grade 3: >50% of vertebral canal stenosis
   e. Grade 4: Extrusion

7. Discospondylitis
   The MR images are subjectively evaluated for the presence of discospondylitis. The criteria for the diagnosis of discospondylitis are according to the following imaging characteristics: (Gendron *et al*. 2012)
   a. Paravertebral STIR hyper-intensity or contrast enhancement.
   b. Hyper-intense signal from the endplates on T2W and STIR images and hypo-intense signal from T1W images.
   c. Contrast enhancement of the vertebral endplates and possible enhancement of contrast in the intervertebral space.
   d. Endplate corrosion
   e. Collapse of the intervertebral space.

## Appendix B

Retrospective pain analysis scoring system.
In case of this research all the patients needed to be scored whether or not they were experiencing low back pain at time of the MRI in relation to the possible presence of Modic changes.

Pain in animals is difficult to recognize. (Mathews 2008) Recognizing pain by the owners is difficult and only vague differences are noticed by them. This information can only be retrieved by a thorough anamnesis. Behavioral changes can be noticed by the owners. For example inappropriate aggressive behavior can stand out. The animal can be reluctant to play or even get aggressive when play is initiated by owners. The owners may mention that the dogs is less active than usual and does not want to go out for a walk or run anymore. Owners from animals with lower back pain often notice that the animal is no longer capable of jumping in the car of walking up the stairs. Stiffness in the hind limbs or even lameness of one of the hind limbs is also a common seen signal by owners. (Mathews 2008, De Risio *et al.* 2000)

Besides collecting signs through anamnesis, clinical examination is also very important to determine whether a dog is suffering from lower back pain.
During the clinical examination of dogs with lower back pain, the pain can be evoked by a couple of tests. Applying pressure on the lumbosacral region is one of these tests which can evoke a pain response from the dog. Another test involves passively moving the lumbar spine and lumbosacral region. There is also test that involves hyperextension of the lumbar spine and simultaneously putting pressure on the lumbosacral region. Also hyperextension of the tail can evoke pain in these dogs with low back pain.
It's difficult to differentiate a pain response that is originating from the lumbosacral region or from the hip joints. Only experienced veterinarians can differentiate between those. (De Risio *et al.* 2000, Meij *et al.* 2010)
There is some literature available that describes the pain experienced by humans due to Modic changes. In this research similar tests have been performed as are available for animals. These test, as for animals, are based on provocation of lumbar pain by pressure and passive movements. The study reported that humans with only degenerative discs show hardly any pain response on these test, while humans with degenerative discs and the presence of Modic changes have significant higher pain responses on all the tests. (Kjaer *et al.* 2006)

For this research the diagnosis of lumbosacral pain can only be based on the retrospectively retrieved history of the patients and the examination findings in Vetware. Because this information will be collected retrospectively there are many disadvantages. The patients are examined by different veterinarians and vet students. Therefore there are many variables in the outcomes of this examination, and drawing conclusions should be done cautiously. To assure that the most reliable information is used from the database only clinical findings of experienced veterinarians and veterinary orthopedic specialists are used. To determine whether the patients used for this research were actually experiencing lower back pain they will be scored using the following scoring system.
A scoring system was set up to score the patients as objectively as possible. The scoring system consists of 7 points of interest from which 4 are non-specific signs which are related to being uncomfortable or pain in the dog. The other 3 are more specific diagnostic tests, as described above, that most clinicians use to evaluate whether a dog is experiencing lower back pain.
The patients are assigned points for every criterion they comply to. Criteria 5 and 6 are the specific tests for low back pain. If the patient complies with these criteria they are assigned more points. These more specific tests are also subcategorized in the reaction that is evoked within the patient. This reaction can vary from slight or doubtful to severe reactions. The different subcategorization of the pain is also rewarded a different amount of points.

1. Unable or reluctant to walk
    a. YES: 1 point
    b. NO or unknown: 0 points
2. Reluctance to jump, climb or walk stairs. Difficulty when standing up or lying down.
    a. YES: 1 point
    b. NO or unknown: 0 points

3. Stiffness or dragging with the hind legs. Lameness of the hind legs.
    a. YES: 1 point
    b. NO or unknown: 0 points
4. Inappropriate or changed behavior noticed by the owners.
    a. YES: 1 point
    b. NO or unknown: 0 points
5. Expression of pain when performing palpation/pressure of the lower back area.
    a. YES: 2 points
        i. Slight or doubtful reaction: 0 points
        ii. Clear painful reaction: 1 point
        iii. Severe reaction: 2 points
    b. NO or unknown: 0 points
6. Expression of pain when performing passive movements and hyperextension of the lumbosacral area.
    a. YES: 2 point
        i. Slight or doubtful reaction: 0 points
        ii. Clear painful reaction: 1 point
        iii. Severe reaction: 2 points
    b. NO or unknown: 0 points
7. Expression of pain when manipulating the tail.
    a. YES: 1 point
    b. NO or unknown: 0 points

A total of 13 points can be rewarded per individual patient. Following the amount of points every patient receives they are classified in one of the three following groups:

| ***Amount of points rewarded*** | ***Classification*** |
|---|---|
| Score ≤ 2 points: | NO. This patient is definitely not suffering from low back pain at this moment. |
| Score 3 or 4 points: | UNDETERMINED. This patient is showing dubious signs which can be related to low back pain but there is no certainty. |
| Score ≥ 5 points: | YES. This patient is definitely suffering from low back pain at this moment. |