University of Veterinary Medicine Budapest
Department of Pathology

Osteoarthritis in dogs
Early diagnosis of canine osteoarthritis prior to the occurrence of irreversible changes

By
Marie Sophie Müller

Supervisor:
Dr. Anna Szilasi
Senior Lecturer

Budapest, Hungary
2023

Abstract

Characterized as a chronic, degenerative, pain-inducing disease of the entire joint organ, osteoarthritis is the most common orthopedic condition in dogs with a major impact on their quality of life. Therapeutic options are very limited, focusing mainly on a palliative management of the disease. Treatment measures cannot interfere with the vicious cycle of ongoing degenerative changes, as the disease can only be diagnosed when it is already relatively advanced. Based on this situation, the objective of this systematic literature review is to evaluate present to futuristic diagnostic methods, in order to determine if the early diagnosis of canine osteoarthritis prior to the occurrence of irreversible changes is possible at the present stage. Furthermore, possibly goal-leading paths are investigated.

The research has revealed, that besides the common imaging tools with their known limitations regarding the osteoarthritis diagnosis, devices with promising potentials are existing. Up to the present state of technological and scientific knowledge, those devices cannot yet diagnose canine osteoarthritis before irreversible alterations start to develop. Consequently, the diseases progression cannot be stopped in time through the application of therapeutic measures, and therefore remains classified as non-curative. Looking ahead, multiple paths were identified that could lead to a breakthrough in early canine osteoarthritis diagnostics. The challenge now is, to select the right approach or combination of approaches and diagnostic methods.

Összefoglalás

Az osteoarthritis a teljes ízületet érintő krónikus, degeneratív, fájdalmat okozó betegségként jellemezhető. Ez a kutyák leggyakoribb ortopédiai megbetegedése, amely jelentős hatással van a kutyák életminőségére. A terápiás lehetőségek nagyon korlátozottak, és főként a betegség palliatív kezelésére összpontosítanak. A kezelés során nem tudunk beavatkozni a folyamat ördögi körébe, mivel a betegséget csak akkor lehet diagnosztizálni, amikor már viszonylag előrehaladott állapotban van. Ebből a helyzetből kiindulva ennek a szisztematikus irodalmi áttekintésnek célja a jelenlegi és a jövőbeni diagnosztikai módszerek értékelése, hogy kiderüljön, lehetséges-e a kutyák osteoarthritisének korai diagnosztizálása a visszafordíthatatlan elváltozások kialakulása előtt.

A kutatás feltárja, hogy az osteoarthritis diagnosztizálására szolgáló, ismert korlátokkal rendelkező általános képalkotó eszközök mellett léteznek ígéretes lehetőségeket rejtő eszközök is. A technológiai és tudományos ismeretek jelenlegi állása szerint ezek az eszközök még nem képesek diagnosztizálni a kutyák osteoarthritisét, mielőtt visszafordíthatatlan elváltozások alakulnának ki. Következésképpen a betegség előrehaladását nem lehet időben megállítani terápiás intézkedések alkalmazásával, és ezért továbbra is a nem gyógyítható kategóriába tartozik. A jövőre nézve több olyan utat is feltártak, amelyek áttörést hozhatnak a kutyák osteoarthritisének korai diagnosztikájában. A kihívás most az, hogy kiválasszuk a megfelelő megközelítést vagy a különböző diagnosztikai módszerek kombinációját.

Table of contents

1 Abbreviations

2D ..... Two-dimensional
3D ..... Three-dimensional
AI ..... Artificial Intelligence
ASU ..... Avocado/Soybean Unsaponifiables
BCS ..... Body Condition Score
BML ..... Bone Marrow Lesion
CBD ..... Cannabidiol
CCL ..... Cranial Cruciate Ligament
COX ..... Cyclooxygenase
CT ..... Computed Tomography
DHA ..... Docosahexaenoic Acid
DJD ..... Degenerative Joint Disease
DMOADs ..... Disease Modifying Osteoarthritis Drugs
EPA ..... Eicosapentaenoic Acid
GABA ..... Gamma-Aminobutyric Acid
GAG ..... Glycosaminoglycan
HA ..... Hyaluronan
HDMPs ..... High Density Mineralized Protrusions
IA ..... Intraarticular
IL-1 ..... Interleukin-1
IM ..... Intramuscular
IV ..... Intravenous
MRI ..... Magnetic Resonance Imaging
n-3 FA ..... Omega-3 Fatty Acids
NMDA ..... N-Methyl-D-Aspartate
NSAIDs ..... Non-Steroidal Anti-Inflammatory Drugs
OA ..... Osteoarthritis
PET ..... Positron Emission Tomography
PO ..... Per Os
PSGAG ..... Polysulfated Glycosaminoglycan

RSO.....Radiosynoviorthesis

SAMe .....S-Adenosyl-L-Methionine

SOD.....Superoxide Dismutase

SYSADOA ..... Symptomatic Slow-Acting Drug For Osteoarthritis

THC .....Tetrahydrocannabinol

TNF-alpha..... Tumor Necrosis Factor Alpha

2 Introduction

Osteoarthritis (OA), also known as Degenerative Joint Disease (DJD) is a chronic, progressive, degenerative and, from a certain point on, irreversible condition of synovial joints. [1] As the disease proceeds, the whole joint including all its components is affected, leading to a "demise of the joint organ" [2]. OA can be characterized in a variety of ways, regarding if it is viewed from a clinical, pathological, histopathological, biomechanical or biochemical perspective for instance. However, the most prominent keywords associated with OA are pain, limitation of movement, cartilage damage, bone remodeling and synovial inflammation. [3] OA can be classified in a primary and secondary form. While the primary form of OA develops idiopathically and independent of predisposing factors due to disturbed cartilage homeostasis associated with ageing, secondary OA results following the occurrence of predisposing factors concerning the articular cartilage and subchondral bone leading to instability or incongruity of the joint accompanied by chronic inflammation. To name a few, such preconditions can be trauma, injury and developmental malformations.

As OA is the most common orthopedic condition observed in canine patients, twenty-five percent of all dogs are diagnosed with OA during their life, while up to sixty percent show radiographic evidence.

Any age, gender and breed can be affected. Due to its severity, long duration and the need of chronic pain management, the disease has a great impact on the animals welfare and quality of life. [2]

3 Objective

Up to this date, OA is still considered as a chronic, degenerative disease which cannot be cured other than through palliative pain management in order to increase life quality. This is based on the fact, that OA can only be definitely determined at a point at which the disease has already progressed and caused irreversible damage to the joint organ. Consequently, the progression has exceeded the sole arthritic stage, an acute inflammatory form, and further has proceeded to a degenerative stage, so-called arthrosis.

Various imaging methods face limitations when it comes to sensitivity and specify of OA diagnostics. Complications of this kind are accompanied by the lack of research for veterinary patients, the need of increased expenses and regulations applying to certain diagnostic tools.

Innovations in OA diagnostics could have multiple positive impacts on the patients condition. Most simple, but most important, the quality of life can be significantly increased through minimizing pain, immobility and lameness plus eventually developing muscular imbalances. Furthermore, disease modifying agents used for medical OA therapy, would have a greater effect in slowing down or even making the degenerative process stop and encourage the regeneration of affected joint components since some changes are still reversible for instance. A final goal would be to close the gap between the current limitations of OA diagnostics and the onset of irreversible changes. Therefore, change the diseases present characteristics to enable curative therapies.

In this systematic review, current to futuristic diagnostic methods for OA will be discussed. Up to the point at which diagnostic methods potentially reach the capability to detect canine OA before the occurrence of irreversible changes within the joint.

4 Pathogenesis

4.1 The healthy joint

The joint is composed of different structures that build up the organ. These are the articular cartilage and the periarticular tissues including the subchondral bone, the synovium which is composed of the synovial lining layer and the subsynovial tissue, the joint capsule, the ligaments, muscles and tendons of the joint. (Figure 1)

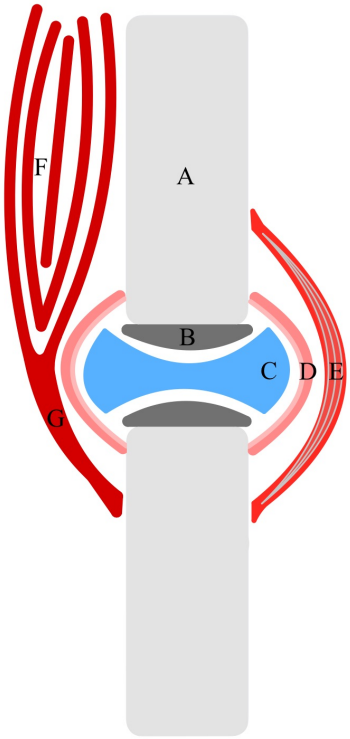

Figure 1 Schematic structure of a healthy synovial joint
(A) bone **(B)** articular cartilage **(C)** synovial cavity filled with synovial fluid **(D)** articular capsule and synovium **(E)** articular ligament **(F)** muscle **(G)** tendon

Under physiological circumstances, these structures with their co-existing characteristics ensure the normal motion and distribution of loads put on it. And thus, its normal function.

The main role of the articular cartilage is the distribution of loads which act on the joint during its normal usage. [4] It is composed of the chondrocytes, the extracellular matrix and consists of eighty percent water. [1]

The cellular part makes up five percent of the total volume. The chondrocytes equally co-existing anabolic and catabolic activities retain the tissues health by a balanced matrix turnover, meaning an equivalent production and degradation, and the ability to adapt to stressors.
They produce collagen and proteoglycans, which make up the major part of the cartilages extracellular matrix. On the other hand, they produce degradation enzymes, the metalloproteases, such as collagenase and stromelysin. Collagenases break down collagen, while stromelysin is being able of collagen and proteoglycan breakdown. [4]
The cartilages matrix consists of type 2 collagen fibres and proteoglycans, hyaluronic acid and glycosaminoglycans for instance. [1] Interlacing collagen fibrils build a meshwork thus provide the cartilage with structure, and simultaneously make it resistant to tractive forces. Proteins with glycosaminoglycan side chains build up the proteoglycans. They have hydrophilic and anionic properties, contributing to the cartilages compressive stiffness.

In the synovium the synoviocytes, the cells of the synovial lining layer, produce synovial fluid which ensures frictionless movement of the joint within its structures. Additionally, the subsynovial layer with its loose connective tissue, small blood vessels and free nerve endings assures the motion between the synovial lining layer and the fibrous joint capsule.

The fibrous joint capsule surrounds the synovium and therefore gives physical stability.

The subchondral bone is a thin bone plate located directly underneath the joint's cartilage. It is normally malleable, which gives it its function as cushioning unit.

Nocireceptors can be found in all articular component tissues except the cartilage. With an increased number, they can be found in the joints capsule. The nocireceptors equip the joint with a warning system by triggering pain due to excessive motion or load. [4]

4.2 The osteoarthritic joint

Events of local inflammation, degeneration and mechanical dysfunction result in a vicious cycle of progressive changes. These changes run parallel, but independent of each other. They are considered to be permanent or only limited regenerative. [4] (Figure 2)

Initial damage to the chondrocytes disturbs the cartilages balance and elicits alterations in its composition. [2, 4] Chondrocytes start to produce inflammatory mediators. Most prominently, the cytokines like Interleukin-1 (IL-1) and Tumor Necrosis Factor Alpha (TNF-alpha). IL-1 is associated with the stimulation of degradative enzyme production. The resulting metalloproteases, collagenase and stromelysin, break down collagen and proteoglycans. Further, the production of proteoglycans is inhibited and fibrous tissue formation in the joints capsule is stimulated. [4] Consequently, the matrix turnover becomes imbalanced, creating good preconditions for the catabolic degradation of the articular cartilage and inhibition of new matrix production. [1, 2]

Abnormal proportions between collagen and proteoglycans can be seen as a consequence of early degenerative changes in the progression of OA. [4] The damaged collagen loses its ability to cross-link and cannot restrict proteoglycans anymore. The hydrophilic proteoglycans absorb water, leading to cartilage swelling. Loads acting on the joint cannot be distributed equally among the cartilages surface anymore but are concentrated on small areas, decreasing its resistance against stress induced damage. [4]

It comes to fibrillation of the cartilages surface, which results in its fragmentation and fissuration. [2, 4] In the later progression of OA, the continued degeneration of the articular cartilage is accompanied by deep cracks and ulceration within the tissue and potentially the complete loss of its surface. [1]

The subchondral bone faces increased stress resulting from the load concentration on the articular surface as an outcome from earlier events. [4] It responds with an increased bone turnover leading to a porous and thinned appearance of the thin bone plate, an increased vascular invasion and bone marrow lesions (BML) in the early progression of the disease. [2] The consequently decreased function as a cushioning unit makes the structure more susceptible to further damage. [4] As OA proceeds, the subchondral bone continues to remodel. Thickening of the subchondral bone plate, trabecular bone sclerosis, subchondral bone cysts and periarticular osteophytes develop in the diseases later stages. [2]

Inflammatory mediators, when generated, affect the neuroreceptors within the soft tissue components that form the joint, resulting in the sensation of pain. Those mediators are algesic substances, which cause direct pain sensation, such as bradykinin, hydrogen ions, serotonin and

substance P, and ones eliciting a pain response by increasing the nocireceptors sensitivity to mechanical and chemical stimuli like prostaglandins, cytokines and leukotrienes. [4]

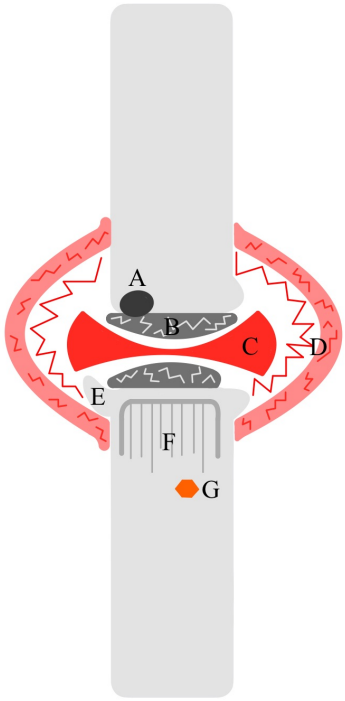

Figure 2 Schematic picture of OA related changes
(A) subchondral bone cyst **(B)** damaged articular cartilage **(C)** narrowed joint space **(D)** thickened articular capsule and inflamed synovium **(E)** bone deformities, osteophytes **(F)** subchondral bone sclerosis **(G)** bone marrow lesions

5 Diagnosis

5.1 The past and the present

5.1.1 Clinical signs

The main clinical sign of dogs affected by OA is pain, observed as abnormal, stiff gait or even lameness. Abnormal sitting, lying and body posture can be seen. Affected animals are often lethargic with difficulties to move.
At physical examination the pain can show as vocalization such as whimpering, aggression or the escape and avoidance of the unpleasant situation. [5] Even though the pathological changes associated with OA are constant, the occurrence of lameness can be of intermitted, gradually increasing or of permanent nature. [1, 4] Its degree can be influenced by resting and exercising periods, as well as by other external factors such as the climate situation, for example. The joint and the surrounding area can have an extended appearance due to its effusion and swelling. Articular thickening and pain contribute to a decreased range of motion of the affected joint. Joint crepitus can be detected as crackling or grating noises. Due to incorrect loading and spare usage of the affected limb, muscular imbalances and degeneration can result as the disease progresses. In addition, signs of the initial cause, for instance injury or developmental abnormalities, can be seen in the cases where OA has developed from such an origin. [1]

A definite diagnosis cannot be made by evaluating the clinical signs only. That is why advanced diagnostic tools, like diagnostic imaging, should be used in addition. Another limitation of using the clinical signs for diagnostics is their relatively late appearance in the progression of the disease. As clinical signs occur, irreversible changes have already developed in the pathology of OA and consequently the success of treatments decreases significantly. [2]

5.1.2 Laboratory investigations

There are no specific laboratory tests for the detection, nor the evaluation of the diseases progression, in the case of OA. Instead, laboratory investigations serve as a tool to rule out other diseases that could mimic the signs of OA, or to find out about the primary underlying

cause of OA in an individual animal. Thus, blood tests can be used to rule out a generalized infection, for instance. [6]

An analysis of the synovial fluid following arthrocentesis can provide information about the inflammatory status of the affected joint. Osteoarthritic joints usually contain an increased fluid volume, therefore a higher number of synovial cells, possibly accompanied by a decreased viscosity. When measuring the cell count, minor increases can be detected. With a predominant increase in mononuclear cells, such as macrophages, lymphocytes and monocytes. And a slighter increase in neutrophil cells. [1, 7] In the case when OA is caused by a previous trauma, red blood cells can be observed during joint fluid analysis. [7]

5.1.3 Radiography

Since the introduction of radiography to veterinary medicine in the 1970s, it remains the number one standard diagnostic and monitoring method in cases when OA is suspected or already diagnosed. [2]

Radiographic imaging utilizes the behavior of ionizing radiation when it is penetrating materials. X-rays are directed onto an object, the body, from which, depending on the tissue, they either get absorbed, scattered or transmitted. The residual emerging radiation is measured, which is the basis for the construction of a two-dimensional image. Based on this principle, radiography is capable of detecting predominately osseous and some soft tissue changes, such as joint space narrowing due to cartilage loss, in the progression of OA. [2, 8] Thereby provides the possibility of an exact diagnosis of OA with the limitation, that this is only an "earlier diagnosis of later stages in OA progression" [2] due to the imaging tools drawbacks that are discussed later.

On a radiographic picture, the disease is marked by periarticular osteophytes, subchondral sclerosis, the joints effusion and swelling, its remodeling and joint space narrowing. (Figure 3) [2] Additionally, if present, sings of other underlying diseases, for example congenital disorders like hip and elbow dysplasia, which may have led to OA, can be seen. [1]

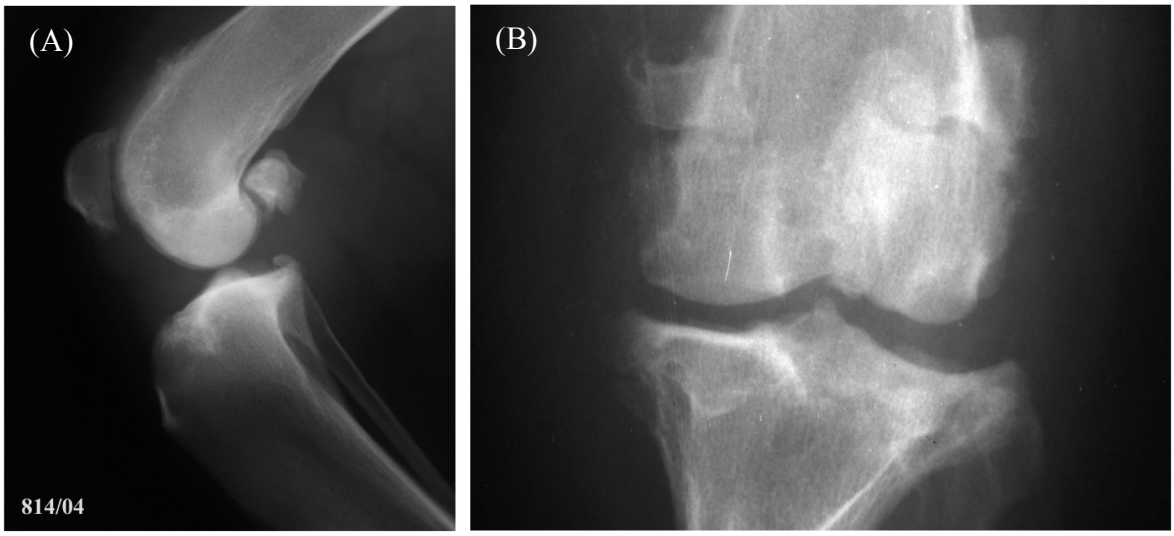

Figure 3 Lateral (A) and caudo-cranial radiographs of a canine stifle affected by OA. Sclerosis, osteophytes and joint space narrowing can be seen. Courtesy of Dr. Attila Arany-Tóth.

The diagnostic value of radiography is restricted by its lack of sensitivity, the very limited range of joint components that can be examined by its use and its few contrast resolutions available.

Radiographic changes and the clinical picture of the disease are not necessarily connected. This has been proofed by force plate analysis and simple observations made by owners and clinicians. [2] It is also insensitive to alterations happening over time as OA proceeds, making it less suitable for the use of monitoring the progression of the disease. [8]

Radiography is only capable to give information about the bony changes and some minor changes of the cartilage and soft tissues. Since this is only a small selection of the components making up the joint and since OA is a condition affecting the entire organ, this characteristic makes the tool less suitable for precise evaluations in the case of OA.

There are only five opacities representing the different contrast resolutions of radiographic imaging: gas or air, fat, fluid or soft tissue, bone and metal. These opacities depend on the tissues natural beam absorption properties and thickness. The problem here is, that the synovial fluid and the cartilage, being a soft tissue structure, have an equal opacity which makes it almost impossible to distinguish between them on a radiographic picture. This weakness can be improved by the use of contrast radiography or anesthetic radiography. For this purpose, contrast material is injected into the joint cavity which changes the radiopacity of the synovial

fluid temporarily, thus making the fluid and the cartilage distinguishable. In the case of anesthetic radiography, a local anesthetic is added to the contrast material to identify the origin and reason of lameness. On the other hand, the use and increase in diagnostic value of those solutions is only limited in veterinary medicine. [2]

5.1.4 Postmortem changes

A variety of macroscopic and microscopic changes can be observed in the joints components at postmortem examination. The expanse of the changes observed is highly dependent on the severity and length of the diseases progression.

Due to degenerative progresses affecting the cartilage, irregular losses can be observed macroscopically. Such losses primarily occur in those areas exposed to intensive loads during motion. (Figure 4) At histopathological examination, fragmentation and fissuration of the cartilages surface can be seen, appearing as vertical clefts or cracks. Furthermore, cloning and apoptosis of chondrocytes can be noticed microscopically. [4] At later stages of the diseases progression, erosion, ulcers and even complete loss of the joints cartilage are possible findings. The initial clefts observed on microscopic examination become deeper. [1, 4]

As the subchondral bone remodels, it appears porous and thinned at early stages of the disease. Additionally, an increased invasion of blood vessels and lesions in the bone marrow can be detected. [2, 4] Later on, the bone appears thickened. Subchondral sclerosis, cysts and bony extrusions, the osteophytes, possibly even osteonecrosis are markers that can be observed at an advanced stage of OA progression. [4]

In the soft tissues composing the joint, such as the synovium, the articular capsule, ligaments and tendons, signs of inflammation are seen. Synovial inflammation shows as thickening of the synovial membrane. Increased fluid production by the synoviocytes makes the affected joint appear effused and swollen. [4]

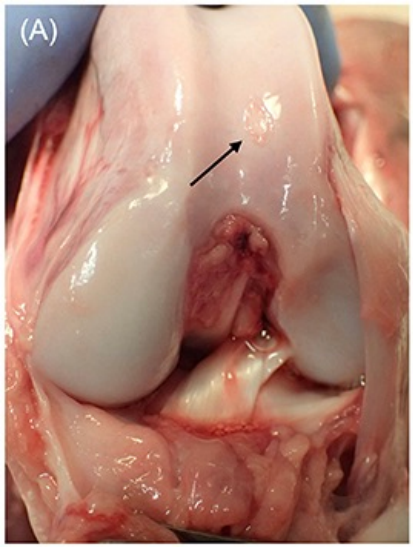

Figure 4 A canine stifle joint at post mortem examination. Damage of the articular cartilage can be observed (black arrow). [2]

5.2 The present and the future

5.2.1 Computed Tomography (CT)

As in radiography, Computed Tomography (CT) uses ionizing radiation to create pictures of predominantly the osseous parts of the body. Following OA is marked by the same characteristics in CT as in radiography. Other than in radiography, in which a two-dimensional (2D) picture is received, with the use of CT a three-dimensional (3D) picture is generated by the reconstruction of cross-sectional images. (Figure 5)

Due to this feature, overlapping structures can be distinguished, which makes the imaging method more sensitive to detect morphological changes of the bone. In OA, such structures are the osteophytes and changes in bone mineral density, referred to as sclerotic areas. Those structures can be used to measure degenerative changes in connection with OA, enabling an earlier diagnosis of the disease compared to radiography. (Figure 6)

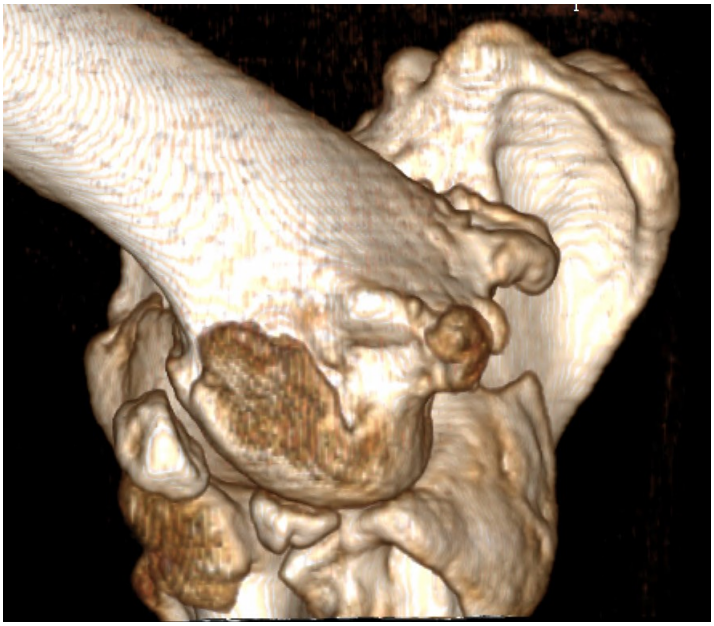

Figure 5 A 3D-reconstruction of an osteoarthritic elbow joint generated by CT-imaging. Osteophytes lying at different levels can be identified. Courtesy of Dr. Attila Arany-Tóth.

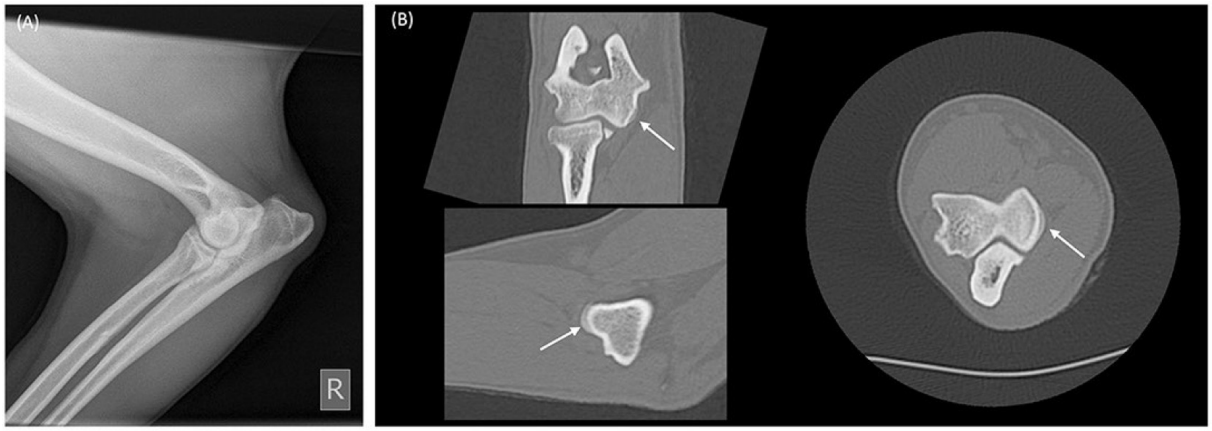

Figure 6 Detection of osteophytes in a canine elbow joint via **(A)** radiography and **(B)** CT **(A)** only minimal evidence of OA can be seen on the medio-lateral radiograph. **(B)** Detection of an osteophyte on the medial humeral condyle in the same elbow via CT imaging. Accordingly, osteophytes can be identified easier and earlier with the use of CT. [2]

Additionally, the Housefield scale, a quantification of radiodensity, expands the opportunities to differentiate soft tissue structures. Yet, the cartilage remains invisible without the use of contrast material. Due to its minimal increase in diagnostic value CT arthrography, CT imaging combined with the administration of intraarticular contrast material injection, is rarely used in veterinary medicine.

On the other hand, micro-CT gives a promising outlook, as it could potentially revolutionize OA diagnostics. It can display structural changes on microscopic level by using slices as thin as five micrometers. Thus, it is expected to reveal early OA biomarkers. On the downside, there are issues with the scalability of scanners and the exposure of patients to hazardous high amounts of radiation. [2]

5.2.2 Magnetic Resonance Imaging (MRI)

By utilizing Magnetic Resonance Imaging (MRI), a 3D picture of anatomical structures, including soft tissues and bone, is created. Thus, MRI is capable to non-invasively and directly asses the whole joint organ. [2, 9]

MRI is based on creating images through a magnetic field, which measures the water content of different structures within the body. And then, based on that, generates a picture.
A water atom consists of one oxygen and two hydrogen molecules. The protons of the hydrogen make it function as a miniature magnet that aligns within the magnetic field of the MRI machine. The hydrogen protons change their direction through the effect of the radiofrequency pulse that disturbs the magnetic field. When the radiofrequency pulse is turned off again, the hydrogen protons return to their initial position. The measurement of the for a certain tissue individual energy levels released, and times taken throughout this progress, enables the creation of an image in which various body tissues can be differentiated. [9] Considering the earlier detection of canine OA, MRI is particularly suitable to picture the joints cartilage due to its high water content (80%).
In contrast to imaging methods using X-rays, lesions observed in MRI pictures are related to the pathological progresses within the joint. Using the right equipment and protocol, a multiplanar, good resolution picture of the articular cartilage ca be produced, making it possible to follow the progression of lesions.
In one of the earliest studies, released in 1987, using MRI to detect alterations in the canine stifle post experimental cranial crucial ligament (CCL) transsection, osteophytes were visible from four weeks after the procedure. While on radiographic pictures, those changes appeared earliest after the twelfth week. This proof an increased sensitivity of MRI in comparison to radiography regarding early OA diagnostics.

Furthermore, early imaging biomarkers were able to be identified with the help of MRI. Bone marrow lesions (BML) are such an early, possibly reversible biomarker (Figure 7). Experimental models, using MRI to analyze dogs after surgical destabilization of the stifle, were able to detect BMLs as early as four to six weeks after the stifle joint has been destabilized. Additionally, BMLs could be found in connection with joint diseases of the stifle and elbow occurring under natural conditions. Other biomarkers, such as high density mineralized protrusions (HDMPs), glycosaminoglycan (GAG) content markers and ones concerning the articular cartilage structure, could be identified in researches for human medicine. Those biomarkers could potentially be adopted in veterinary medicine, making the diagnosis of OA imaginable at earlier stages.

The above-mentioned findings strengthen the assumption that with the right imaging method even earlier biomarkers could possibly become detectable and consequently an even earlier detection of OA. [2]

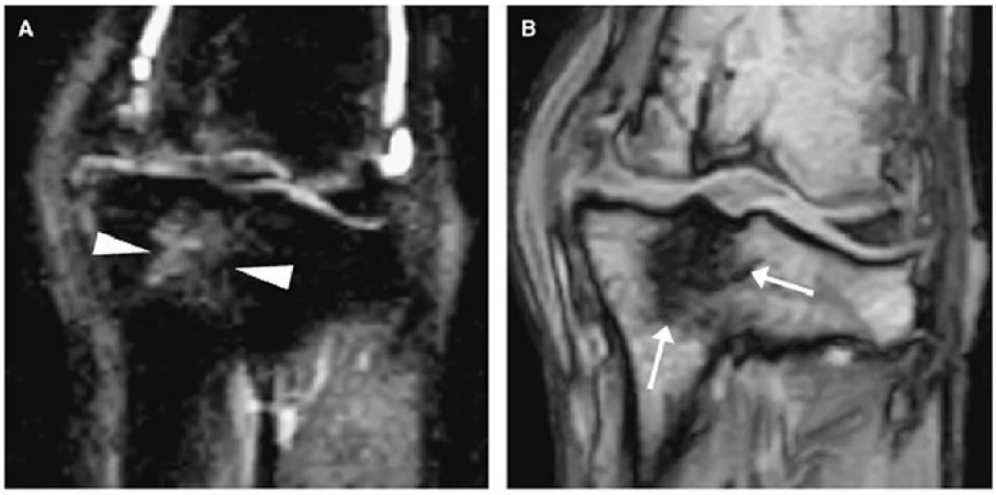

Figure 7 A bone marrow lesion (BML) on the dorsal aspect of the tibia of a canine stifle joint (arrows). BMLs are considered as an early imaging biomarker of OA that can be identified with MRI. [2]

On the downside, MRI comes with features like high costs, limited availability, long procedure times and the necessity of general anesthesia in order to reduce movement artefacts while the image is taken. Based on that, MRI could not compete yet with the already well established imaging methods, radiography and CT, that are widely used for the diagnosis of canine OA in veterinary medicine. [2]

5.2.3 Nuclear medicine

Another approach to make an earlier canine OA diagnosis possible could be the imaging of metabolic alterations of involved tissues, instead of the sole analysis of morphological scans. Since those metabolic alterations are known to go ahead of structural changes, such an approach could potentially introduce new opportunities in early OA diagnostics. [2]
Imaging tools of nuclear medicine, like gamma scintigraphy and positron emission tomography (PET), make use of the properties of radioactive isotopes. Radiopharmaceuticals are introduced into the body and, within it, are attracted by certain target structures, creating a so-called hot spot. The radiation emitted from those radioactively tagged hot spots is then measured by a special camera and a functional image is created. [10]

Gamma scintigraphy uses radionuclides emitting gamma radiation, most commonly Technetium-99m. Phosphate bound Technetium-99m has shown a marked uptake in regions with increased osteoblast activity, hence in bones with an increased activity of remodeling. [2, 10] In the OA joint, an early and a late phase pattern can be differentiated. While the early phase pattern indicates synovitis, the late phase pattern marks the osteophyte formation in the progression of OA. [2] *In-vivo* uptake of chondroitin sulfate bound Technetium-99m has been examined in dogs that were already diagnosed with OA. After the intravenous (IV) administration of the radiopharmaceutical, significant hot spots could be determined in those joints affected by the disease. [11]

PET works by the same principles as the gamma scintigraphy, but instead of gamma radiation emitting, positron emitting radiopharmaceuticals are applied. Most frequently, Fluorine-18 is used for that purpose.
The administration of the glucose analogue Fluoro-2-Deoxy-D-Glucose has shown to be reliable in the examination of lameness originating from a soft tissue issue. Apart from that, sodium fluoride Fluorine-18 has proven to be a biomarker for metabolic processes of the bone. An experimental model investigating the use of nuclear medicine for canine OA diagnostics has shown an increased uptake of the substance between the third and the twelfth week after the surgical intervention. [2]

It is advisable to complement the functional scans of the imaging tools discussed with anatomic scans of the structure. Combined PET/CT and PET/MRI machines are already available for that purpose. [2, 10] (Figure 8)

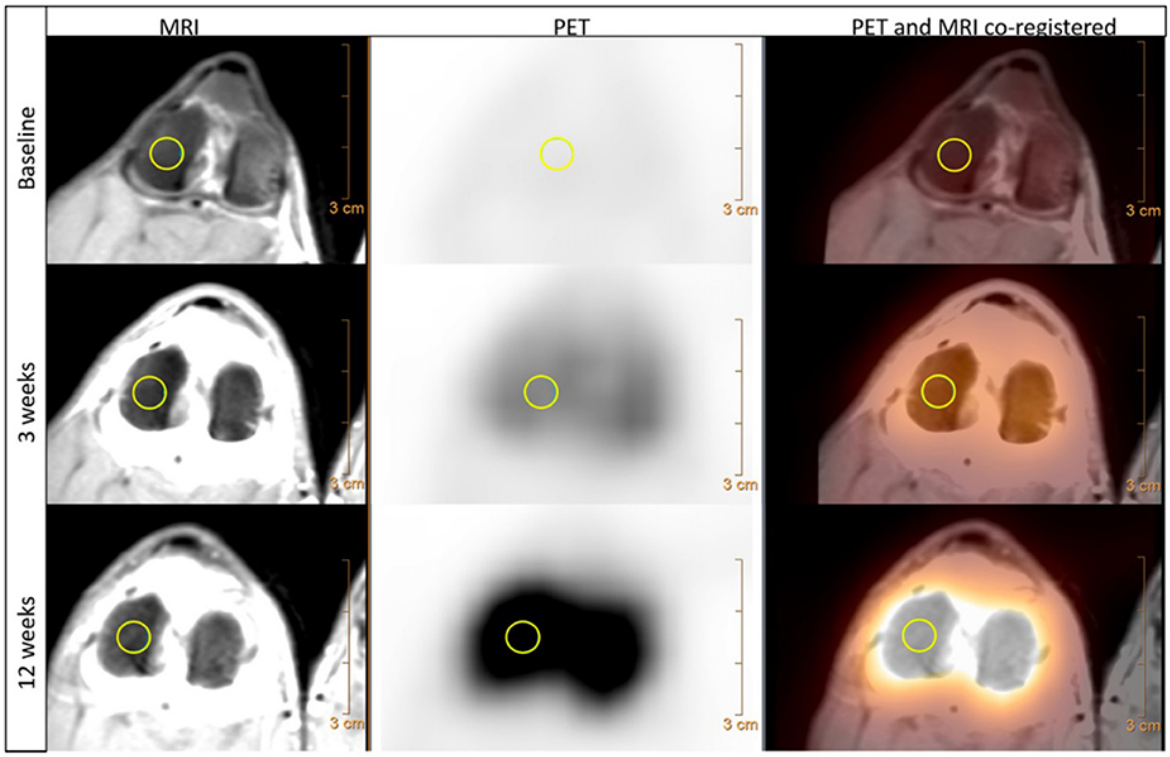

Figure 8 MRI (first column), PET (second column) and combined PET/MRI (third column) transverse projections of the canine stifle before, three weeks and twelve weeks post CCL transsection. [2]

Although diagnostic imaging using nuclear medicine has proven its sensitivity in the detection of early OA biomarkers and shown to be a promising tool for the diagnosis of early OA in dogs, it is mainly used for research purposes. This is due to the requirement of further research on the one hand, on the other hand, it is difficult to be integrated into daily clinical practice since it is accompanied by a poor specify, strict regulations applying to radiopharmaceuticals, high costs and the challenging interpretation of results. [2, 10]

6 Treatment

6.1 Approach

OA is a on multiple levels progressive disease in which the damages, except the earliest, are considered as irreversible. [4] Consequently, no specific nor curative therapies are available. Therefore, the goals of the therapy, until the gap between the occurrence of irreversible alterations and the earliest diagnosis possible can be closed, are based on increasing the animals life quality by minimizing the progression of the pathological changes and by providing support through pain relieving measures and the built-up of joint function as far as possible. [1, 5] The progressive pathological changes are regarded as independent of each other. That's why a combination of approaches, a so-called multi-modal approach, for the treatment of clinical signs and pathological changes should be applied. [1, 4] Such an approach addresses the animals way of life by body weight optimization and controlled exercising. In combination with feed supplements, pharmaceuticals and finally surgical solutions taken into account when creating the therapeutic plan. A pyramid-like system can be used to adjust the intensity of the therapy to the degree of OA. [4] An example can be seen in the figure below. (Figure 9)

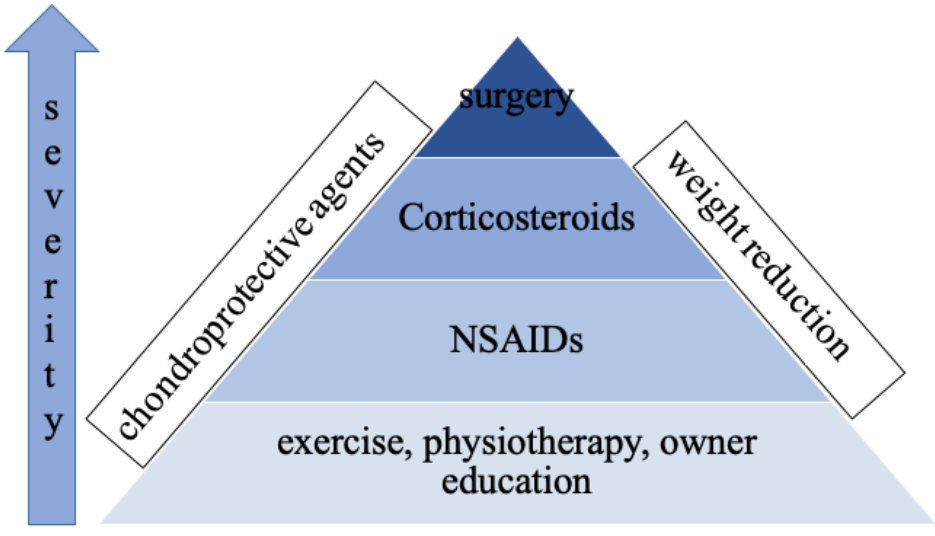

Figure 9 A pyramidal approach for the therapy of OA. Accordingly, more severe affected animals are treated more intensive, while animals with only mild symptoms are treated less aggressively.

6.2 Nonmedical treatments

Weight optimization and exercise are referred as the nonmedical strategies of OA therapies and built the base of every effective treatment. Nevertheless, they are often neglected as they are overshadowed by rapid effects of drug therapies. [4] To ensure their effectivity, owner education plays a crucial role. As well as the animal keepers motivation and willingness to learn. [12]

6.2.1 Weight optimization

Weight optimization is considered as a key factor in the management of OA. It means, on the one hand, weight reduction of obese animals, on the other hand, avoidance of too rapid growth of young animals during their first year of life which could trigger developmental disorders. [12] Although OA is not caused by excessive body weight, it shows an increased prevalence in obese animals. This can be explained by the fact that increased weight means increased stress on the joint, hence increased mechanical damage accompanied by a faster progression of the disease. [4, 5, 12] Studies of the Arthritis Foundation have shown that an increase of one pound in body weight consequently raises the load put on the knee to three pounds and those put on the hips to six pounds. [5] Pro-inflammatory metabolic activities that are carried out by the adipose tissue enhance the already existing inflammatory changes, thus the speed of the diseases progression. In addition, the lethargy of overweight animals often leads to further weight gain and consequently to further aggravation of the joints condition. [1]

In contrast, reduction of the body weight can decrease the mechanical loads acting on the joints structures and attenuate clinical signs. Even a reduction of only six percent of the body weight can improve the clinically observed degree of lameness, and contribute to minimizing drug doses. [1, 5]

After the estimation of a body condition score (BCS) for the individual patient, the optimal body weight should be determined, and a weight loss program set based on those values. [1] A restrictive diet promoting weight loss should be of high protein and low fat content. And most importantly, should have a negative energy balance. [5]

6.2.2 Exercise

Regular and long-term exercising can support body weight loss of obese animals. Apart from that, it increases the joints mobility and strengthens the musculature and supporting tissues of the joint organ, enabling a better transmission and distribution of loads acting on the joint. [5] It may even be, that the cartilage is left out in the transmission of loads. [4] Additionally, exercise tolerance can be increased. [1] When developing an exercise plan, the individual health condition of the animal should be taken into account. [12] In most cases, low to medium impact activities are appropriate. Such exercises could include walking, swimming or training on an underwater treadmill. Using an underwater treadmill ensures a minimal impact of forces acting on the joint. [5] Therefore, it is especially appropriate for dogs that are severely affected by OA. [12]

6.3 Medical treatments

A variety of drug-based treatment options is available for the medical therapy of OA. In accordance to the stage of progression and severity of the disease in the affected animal, a less or more intensive medical approach can be chosen.

6.3.1 Chondroprotective agents

Chondroprotective agents, also referred to as Disease Modifying Osteoarthritis Drugs (DMOADs), are commonly used pharmaceuticals in order to avoid, decrease or even repair cartilage damage. This is enabled by their ability to increase synoviocytic as well as chondrocytic activities, provide matrix support and decrease cartilage breakdown. Due to their potential to reduce inflammatory mediators, they are said to have anti-inflammatory properties. [1, 3] Despite their questionable effectivity from certain points of views, they are nevertheless popular because of their potential beneficial characteristics combined with a relatively high safety. [1, 3, 4] Substances having such properties belong to the group of glycosaminoglycans. Naturally, they are a major cartilage component, responsible for the maintenance of its health. [5] DMOADs are either for oral administration, considered as food additives, or for parenteral use. [3]

The most popular are the orally administered Glucosamine and Chondroitin Sulfate. [4] They promote synovial fluid synthesis, and therefore they are beneficial for the joints lubrication, encourage cartilage regeneration and prevent its degeneration. In addition, they have anti-inflammatory properties through limiting degradative enzyme synthesis and chondrocyte apoptosis. [1, 5]

Glucosamine (2-Amino-2-Deoxy-D-Glucose) is the precursor for the synthesis of glycosaminoglycans. It is a naturally occurring monosaccharide, consisting of sugar and amino acids. There are three forms: Glucosamine Sulfate, Glucosamine Hydrochloride and N-Acetyl Glucosamine of which the former, Glucosamine Sulfate, is the primary choice for OA treatment as it contains sulfate which is needed for cartilage formation. Nutraceuticals containing Glucosamine are extracted from crustaceans chitinous exoskeletons or from fermented grains, such as corn and wheat. When used at their recommended dose, they are considered as relatively safe since they have only minor short-term side effects, for example gastrointestinal signs like diarrhea and constipation, headache and urticaria, and no known long-term side effects at all. In contrast, when they are overdosed, pancreatic cell damage and an increased diabetes risk can occur. In oral formulations, Glucosamine is often combined with Chondroitin Sulfate. It is one of the most common glycosaminoglycans that can be found in the articular cartilage, and, in that sense, essential for the maintenance of its health. As Glucosamine, it is considered as relatively safe. [5]

On the downside, glycosaminoglycans have a questionable bioavailability when administered orally. Studies demonstrated a bioavailability of twelve percent for Glucosamine and five percent for Chondroitin Sulfate after a single oral administration of Consequin, an oral formulation containing 600 mg Glucosamine Hydrochloride and 300 mg Sodium Chondroitin Sulfate per tablet. The bioavailability of Chondroitin Sulfate increased with repeated application, reaching up to seventy percent. [3, 5] Considering that, it must be taken into account that the mentioned concentrations were found in the blood, which makes the bioavailability and effectivity in the actual target tissues questionable. [3]

In contrast, the effect of injectable glycosaminoglycans is more reliable. This group includes Polysulfated Glycosaminoclycan (PSGAG). It is a combination consisting of highly sulfated glycosaminoglycans out of which Chondroitin Sulfate is the major ingredient. It is obtained by extraction from cartilage of the bovine respiratory tract. [3] Several studies prove its efficiency when injected following early diagnosis of OA. *In-vitro* studies have demonstrated its

capability of inhibiting degenerative enzyme synthesis, thus the limitation of cartilage degeneration. Others evince their anabolic effect beneficial for the cartilages structure and function by enhancing protein, collagen, proteoglycan and hyaluronic acid production. [1, 3] *In-vivo* experiments verified their broad distribution in the target tissues following intramuscular (IM) injection. Furthermore, disease modifying characteristics were confirmed as young dogs diagnosed with hip dysplasia and treated with PSGAGs turned out to have a better hip conformation when fully grown as the ones that did not receive any treatment. Besides that, dogs with radiological confirmed OA treated with Adequam, a formulation for IM injection containing 100 mg/ml PSGAG, once per week, over a period of four weeks responded with an improvement of the clinical observed lameness.
PSGAGs are not recommended to be used as intraarticular (IA) injection, especially directly following joint surgery, and for the use in animals with confirmed coagulation disorders. Similar to Glucosamine and Chondroitin Sulfate, the efficiency of PSGAGs when given orally as nutraceutical is variable. [3]

Another DMOAD which is mainly used as an injection, not orally due to its limited bioavailability and efficiency, is Hyaluronan (HA). HA is a non-sulfated glycosaminoglycan. It is regarded as a Symptomatic Slow-Acting Drug for OA (SYSADOA) with joint lubrication properties. [1, 3] Following single or multiple IA injections, long-term improvements of dogs affected by OA could be observed. A disadvantage to be considered is the risk of iatrogenic infection due to its need to be injected directly into the joint. [3]

6.3.2 Non-Steroidal Anti-Inflammatory Agents (NSAIDs)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the most common drugs of choice for the treatment of canine OA. Their immediate analgesic, anti-inflammatory and -pyretic properties cannot be outweighed by their potential toxicity and occurrence of adverse effects. Side effects in connection with the administration of NSAIDs can affect the gastrointestinal, hematopoietic, hepatic and renal systems. [1, 4] Even though the known side effects are limiting their use, NSAIDs long-term therapy is not associated with an increasing occurrence of their side effects. [1] NSAIDs exhibit their analgesic, anti-inflammatory and -pyretic characteristics by the inhibition of cyclooxygenase (COX) enzymes, COX-1 and COX-2, in the pain pathway of arachidonic acid. COX enzymes are responsible for the bodys prostaglandin production. The

resulting prostaglandins can be either beneficial or harmful for the body. While COX-1 contributes to a normal body function by regulating platelet aggregation, gastric mucus and acid secretion and maintaining gastric and renal blood flow, COX-2 mediates inflammation, pain and fever. When using NSAIDs for the treatment of OA, the aim is to rather inhibit COX-2 than COX-1 or both. [1, 13]

There are several agents that can be used for the OA therapy of dogs. The adequate agent for the individual patient should be selected based on the response, cost, dosage, timing of administration and side effects of the product. [4] Additionally, it is crucial to be aware that NSAIDs should not be combined with each other, neither with Corticosteroids. [13]

The non-prescription NSAID Acetylsalicylic Acid (Aspirin) is a long and commonly used drug, considered as effective in the treatment of OA. On the downside, its high probability to cause gastrointestinal adverse effects, including gastric irritations, erosions and ulcers, and bleeding disorders reduce its popularity.

With an increased safety, efficiency and suitability for acute and chronic pain management, the prescription NSAIDs outdo the non-prescription NSAIDs in being adequate for canine OA treatment. Three groups can be differentiated according to the agents capability to only inhibit COX-2. The COX-preferential NSAIDs: Carprofen, Etodolac, Meloxicam, the COX-selective NSAIDs also referred as Coxibs: Deracoxib, Robenacoxib, Firocoxib and the Piprants with Grapipitat as the sole representative. [4, 5, 13] Unlike the conventional NSAIDs, Grapipitat acts as an EP 4 prostaglandin receptor antagonist at a later point of the arachidonic acid pathway. Thereby, it spares the COX-1 blockage and the associated side effects completely. However, the different mechanism of action makes it less efficient for acute, but suitable for chronic pain management. [1, 13]

6.3.3 Corticosteroids

Corticosteroids are apt pharmaceuticals to use in the case of acute deterioration of clinical signs in a dog suffering from OA. [1, 4, 5] Like the NSAIDs, they act on the arachidonic acid pathway. But other than the NSAIDs, Corticosteroids unfold their analgesic and anti-inflammatory abilities by blocking the arachidonic acid production, thus inhibiting

prostaglandin synthesis and inflammation. Corticosteroids, such as Cortisone, are naturally occurring steroid hormones. They are normally produced by the cortex of the adrenal gland. Artificial products, like Hydrocortisone and Prednisolone, used for medications, have a five to six times stronger effect compared to the naturally synthetized hormone. [5]
The use of steroidal drugs should be limited and preferably only be administered for short-term, with a maximal length of three to four months of treatment. Either local, as IA injection, or systemic as an oral medication. [1, 4, 5] When applied directly into the joint, Corticosteroids are potential chondrotoxic and can induce osteoporosis of the subchondral bone. Furthermore, there is a risk of iatrogenic infection of the joint. [1, 4] Since Corticosteroids affect a wide range of tissues, per os (PO) administration is used for several indications. For instance, in the case of immune mediated diseases or inflammation. Generally, low doses are given to cure inflammations, while administration of high doses affect the immune system. [5]
Side effects of Corticosteroids depend on the dose and duration of their administration. Typically, a high incidence of systemic adverse effects is connected to long-term use or high dosages. [4, 5] Those side effects include: osteoporosis of the bones; gastrointestinal bleeding and ulcers; immunosuppression; body weight gain, fluid retention and increased blood sugar levels, also referred to as Cushing syndrome. [5] As mentioned for the NSAIDs, Corticosteroids should not be combined with NSAIDs since there is an increased probability of gastrointestinal toxicity by doing so. [4]

6.3.4 Other analgesics

Analgesics which relief pain only, thus have no properties to alter the course of OA, can be components of the multi-modal OA treatment. Usually, they are ancillary to NSAIDs, which have disease modifying properties through their anti-inflammatory action. [1, 13] In some cases, when the administration of NSAIDs is contraindicated, they can also serve as an alternative. [1] It is important to precisely adjust the dose for the individual animal to avoid sedation, being their major side effect. [13]

Gabapentin is one drug that can be used for such indication. It is considered as an antiepileptic with pain relieving attributes. Especially the relief of neuropathic pain, which often contributes to chronic pain. [1, 4, 14] The structure of Gabapentin is similar to the neurotransmitter Gamma-Aminobutyric Acid (GABA). It functions by inhibiting presynaptic calcium channels,

followed by a decreased release of neurotransmitters and consequently decreased pain sensation. [14] Even though Gabapentin usage in dogs is off-label, it is widely used for the control of chronic pain, administered in the form of oral preparations. A precise dose adjustment and regular administrations, at an interval of six to eight hours, are essential to ensure its desired action. The occurrence of adverse effects is uncommon, chiefly in the long-term usage of Gabapentin, and usually dose-linked. Sedation is the major side effect noted. It can usually be eliminated by readjustment of the dose. [1, 14] Predominantly in old and weak animals, ataxia and weakness can be seen as an adverse event. [14]

Amantadine is another pharmaceutical that can be used off-label in canine patients for the management of moderate to severe pain in OA. It is particularly suitable for the treatment of so-called wind-up pain. Wind-up pain describes a central hypersensitivity, resulting from nerve sensation due to prolonged pain. As a consequence, normal stimuli become painful events. [13] Amantadine works as an N-Methyl-D-Aspartate (NMDA) receptor antagonist in the central nerve system, hence has the ability to block or reverse sensitization of central pain. [1] Based on its mechanism of action, Amantadine is defined as an antihyperanalgesic. [14] For that reason, it is advisable to combine it with a true analgesic, like the NSAIDs. [1, 14] A study has proven that the joint administration of Amantadine and NSAIDs significantly improved the activity and lameness scores in dogs with OA compared to dogs treated with NSAIDs only. Due to its characteristics, it is often used as a supplementary drug in case of deterioration of chronic pain. The application should be done twice daily for a minimum period of twenty-one days. It can be extended for lifetime if necessary. [14] Other than an undesired sedation when used in combination, no side effects or drug interactions have been recognized. [4, 14]

6.4 Alternative treatments

As osteoarthritis is a progressive chronic disease requiring long-term treatment, alternative treatment options are becoming increasingly popular.
Those can be taken into consideration as a supportive measure or in order to replace a certain conventional treatment. The range of alternative treatment options regarding OA are of various natures. In the following, a selection of such alternatives is discussed.

One possibility are direct physical measures, like physical therapy, acupuncture or the use of different therapeutic energy modalities applied to the body. [1]

As already mentioned, as the nonmedical treatments were discussed, using controlled exercise in order to support dogs affected by OA, physical therapy applying specific patterns of motion can support those aims. Thus, physical therapy can contribute to body weight loss, increased joint mobility and muscle strength. [3, 5] Affected joints can therefore benefit from better transmission and distribution of loads due to improved joint support. [3] Different practices of acupuncture can serve as an alternative approach to conventional treatment methods of OA. [1] However, studies evaluating the effectivity of acupuncture in natural occurring canine elbow OA have shown that the improvements observed were rather of subjective nature than an actual increase in objective scientific parameters. [15] The same applies to a variety of energy modalities applied to improve clinical signs of dogs affected by OA. Such energy modalities include for example shock wave and laser therapies, therapeutics using pulsed electromagnetic fields, curative ultrasound and electric nerve stimulation through the skin. [1]

Nutraceuticals also referred to as food additives or supplements, are usually based on plants or another natural product. Typically, they elicit multiple effects within the body, instead of being restricted to one specific action. Regarding OA, the nutraceuticals used are desired to have generally antioxidant or anti-inflammatory properties or both. While the effects of food supplements are considered as limited after a typically slow onset of action, they have shown to be safe by having minimal to no adverse effects. [5, 13]

Omega-3 Fatty Acids (n-3 FA), in particular Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA), have proven to have anti-inflammatory effects after a minimum administration of one month. [1, 13] Studies analyzing the effect of n-3 FAs in OA dogs, have confirmed the nutraceuticals effectivity. Accordingly, clinical signs were decreased, so that even reductions in NSAIDs dosages could be made. [1, 12] To reach the desired actions, long-chain fatty acids should always be preferred over short-chain fatty acids. This is based on the increased bioavailability of long-chain fatty acids derived from cold water marine mammals in carnivores, compared to short-chain fatty acids that are usually plant-based. [1] However, it is important to be aware that cod liver oil should be used with caution as it could possibly lead to vitamin A toxicosis. [13] Regarding the dose, the preferred ratio of DHA to EPA is 2:3.

Like the n-3 FAs, Green Lipped Mussel Extract has shown to be anti-inflammatory by interfering with the inflammation cascade, after being used as a food supplement for several weeks. [1, 13]

Cannabinoids are obtained from hemp plants. They are characterized by their anti-inflammatory and anti-oxidant features, as well by their ability to decease pain perception. [13] A study has verified decreased signalment of pain and increased mobility, after the oral administration of Cannabidiol (CBD) in dogs affected by OA. [1] In canine patients, products containing low Tetrahydrocannabinol (THC) levels, based on whole hemp, are the only ones that can be used legally for therapy. Further, it has to be mentioned that CBD induces enzymes of the liver, which could potentially interfere and decrease the effects of other medications given to manage the disease. This is particularly important considering that the treatment of OA is based on a multi-modal approach. [13]

Equipped with anti-inflammatory abilities, by suppressing prostaglandin production via gene suppression, as well as antioxidant properties, Polyphenols can contribute to an alternative approach in OA treatment. The group of Polyphenols includes substances such as the spirula algae derivate Phycocyanin, Grape Seed Oil, Green Tea Extracts and Turmeric. [13]

Avocado/Soybean Unsaponifiables (ASU) are extracted from the respective plant, and separated from their fats. [13] ASUs have demonstrated anti-inflammatory features when used as a food additive. In addition, they may contribute to the protection and repair of the joint by reducing degradative enzymes. [12, 13]

Comparable actions are characteristic for dried milk proteins. Dried milk proteins are produced from “anti-inflammatory milk”, obtained from hyperimmunized dairy cows. Those dried milk proteins are then used as an ingredient of medical treats. [13]

Beyond the above-mentioned active substances, various others can be beneficial to manage canine OA using alternative treatment methods. This includes common anti-oxidants, like vitamin A and C, S-Adenosyl-L-Methionine (SAMe) and Superoxide Dismutase (SOD) besides many more. [13]

6.5 Novel treatments

So far, OA is classified as a non-curable disease that requires a palliative, permanent and long-term multi-modal therapy. This therapeutic approach often faces limitations as painkillers reach ceiling effects, and following decreasing their analgesic effectivity despite increased doses. This is why research is constantly being conduced into new treatment options. Some of these options are presented below.

Intraarticular (IA) injection of autologous cells has shown to offer one option. Those cells can either be stem cells, obtained from the patients tissues, or platelet rich plasma, derived from the blood. [13] In the case of IA administration of mesenchymal stem cells into the affected joint, the cells are extracted from the animals adipose tissue or bone marrow. Although the extraction of cells from both tissues requires a surgical procedure under general anesthesia, the extraction of stem cells from fat is considered as less invasive, thus the first choice. [5, 13] The separation of stem cells from the tissue is followed by their expansion in cell cultures. Finally, the cells are injected into the joint, in which they release substances with anti-inflammatory and cartilage repair properties, leading to improved clinical signs. The exact mode of action elicited by the IA injection of autologous mesenchymal stem cells is not fully understood yet. A benefit of this therapy using the body's own cells is that the risk of rejection remains relatively low. [5]
The IA administration of platelet rich plasma follows the same principle as the mesenchymal stem cells. Cells are obtained from the patients own blood. After the isolation of platelets from red and white blood cells, a plasma high in active platelet concentration is obtained. A so-called platelet-rich plasma. Besides the usually associated blood clotting properties of platelets, they additionally promote growth and healing of tissues, contributing to the joints regeneration. [13]

Apart from the IA injection of autologous cells, the administration of radiopharmaceuticals has proven to be effective in canine OA therapies. [1, 16, 17] Such treatment, a so-called radiosynoviorthesis (RSO), can be provided by the product Synovetin OA. Which is, until now, only licensed for canine elbow OA. [13]
When treating an osteoarthritic joint with Synovetin OA, Tin-117 radioisotopes are injected into the articular capsule. Low-energy conversion electrons are given off within the injected joint. This is why the therapy is also referred as conversion electron treatment. Those emitted electrons target synoviocytes and macrophages, from which they get absorbed. The absorption

is followed by apoptosis and reduced concentrations of inflammatory cells. [1, 18] The manufacturer of Synovetin OA assures the product to have a long-lasting analgesic and anti-inflammatory action, accompanied by decreased clinical signs and increased mobility. Additionally, it has disease modifying properties. [18] Studies have investigated the therapies effectivity for different severity grades of natural canine elbow OA. In mild to moderate cases of grade one and two OA, ninety-two percent of the treatments were successful. [16] While in more advanced cases, affected by grade three elbow OA, seventy-one percent of the treatments could be considered as effective. [17] Additional to the already mentioned actions, there are further advantages, such as the radiopharmaceuticals long-term effectivity and safety of application. Due to the long-lasting action of Synovetin OA, which can extend up to one year, it has to be administered once a year only. [1, 18] Furthermore, the safety of the product has been proven, even after repetitive administrations. [19] On the downside, difficulties potentially have to be faced when it comes to regulations for radiopharmaceuticals, as already mentioned for other diagnostic and therapeutic approaches using radioactive substances. [1]

6.6 Surgical treatments

Surgical interventions become an option, when OA has severely progressed and medical treatments cannot reach their desired actions anymore. [1] In contrast to a therapy based on pharmaceuticals, a surgical treatment can be a solution to cure the primary cause eliciting OA. [1, 4]

A total joint replacement can be done to correct the morphology of anatomic structures in case of congenital defects, such as hip or elbow dysplasia. [1, 4] That way adequate pain relief and joint function can be provided. [4] Unfortunately, such a method is only available for the canines hip joint, referred to as total hip arthroplasty. [1, 4] Modification of the joints morphology can also be achieved via arthroplasties using resection or excision techniques for reconstruction. In addition to the hip joint, such techniques are also available for the elbow joint of dogs. [4]

To treat cases in which OA is primary caused by joint instability, arthrodesis of the affected joint can serve as an option to restore sufficient stability. Due to the joints stiffening resulting from this surgical intervention, the functionality of the treated joint is considered as limited as

outcome of the procedure. [4] Instabilities can also be solved by the repair of underlying lesions. For instance, by performing an osteotomy- or suture-based technique in a dog with a ruptured cranial cruciate ligament. [1]

7 Results

To come back to the initial central question of this review, regarding the early detection of canine OA prior to the occurrence of irreversible changes, and therefore the breakthrough in switching the diseases characteristics to being curable. According to the results of this systematic literature review, the present situation can be described as in the following.

The most widespread diagnostic tools used related to canine OA nowadays are the X-ray-based radiography and CT. Even though they are restricted to only a minority of the compartments forming the joint, they can provide a definite diagnosis. On the downside, this diagnosis can only be made at a relatively late stage of the diseases progression, as those methods mainly focus on bony alterations. At the time such changes can be detected, they cannot be reversed through the application of therapeutic measures anymore. Rarely used contrast and anesthetic radiography and CT methods are able to partially lift some limitations regarding the tissue types that can be visualized by providing the possibility to differentiate between synovial fluid and cartilaginous tissue. On the other hand, this improvement is not enough to enable the detection of OA before the onset of irreversible changes. With the micro-CT, CT provides a promising innovation. If drawbacks regarding its usage in animals can be solved, it might be a significant door-opener in early OA diagnostics. [2]

Advanced imaging methods based on other principles than radiography offer a promising potential for early canine OA diagnostics. Such methods include MRI and the nuclear medicine-related, gamma scintigraphy and PET. Through the evaluation of the water protons movement within a magnetic field, MRI can image the whole joint organ with all of its components.[2, 9] Due to its high water content, cartilage tissue in particular can be imaged very well. On top of that, MRI has shown an increased sensitivity in comparison to radiography and CT regarding the early detection of OA. This has been proved by studies, in which MRI was able to detect OA related changes in one third of the time that radiography required to make a definite diagnosis. Furthermore, possibly reversible biomarkers related to early OA changes, the BMLs, could be identified with the help of MRI imaging. The identification of further biomarkers in human medicine, such as HDMPs, GAG-content related and ones concerning the cartilage structure, and the possibility of adopting them into veterinary medicine, provide a promising outlook in the future. [2]

Methods of nuclear medicine use a whole different approach of diagnostic imaging, which makes them superior in some aspects. With the injection of radiopharmaceuticals and the creation of so-called hot spots, instead of a structural, a functional picture is created. Since those metabolic abnormalities appear before the development of morphological changes, OA can be detected at a relatively early stage in the progression of the disease. [2] Gamma scintigraphy is capable to display the osteoblast activity of the bone. [2, 10] Related to OA, patterns of the early, representing synovitis, and late phase, depicting osteophyte formation, can be differentiated. Especially, the identification of synovitis could serve as an indicator for early, possibly reversible state of OA with an acute inflammation of the synovial fluid. [2] Other, cartilage bound radioisotopes can display abnormalities related to the cartilage, in which some of the earliest changes appear. [11] Comparable to gamma scintigraphy, PET can detect alterations in the bone and soft tissues composing the joint organ and is therefore equipped with the same promising properties in relation to early canine OA diagnostics. Even though their increased sensitivity for early OA biomarkers, the radioisotope-based methods are lacking in specifity when it comes to making a reliable, definite diagnosis of OA. Although MRI, gamma scintigraphy and PET offer various advantages, they were unable to compete with the commonly used X-ray-based methods to date, and therefore are only rarely used in veterinary medicine. On the other hand, further research related to veterinary medicine, improvements and solutions for current weaknesses could lead to a major breakthrough in diagnosing reversible changes in canine OA patients with the use of the above-mentioned advanced imaging methods. [2]

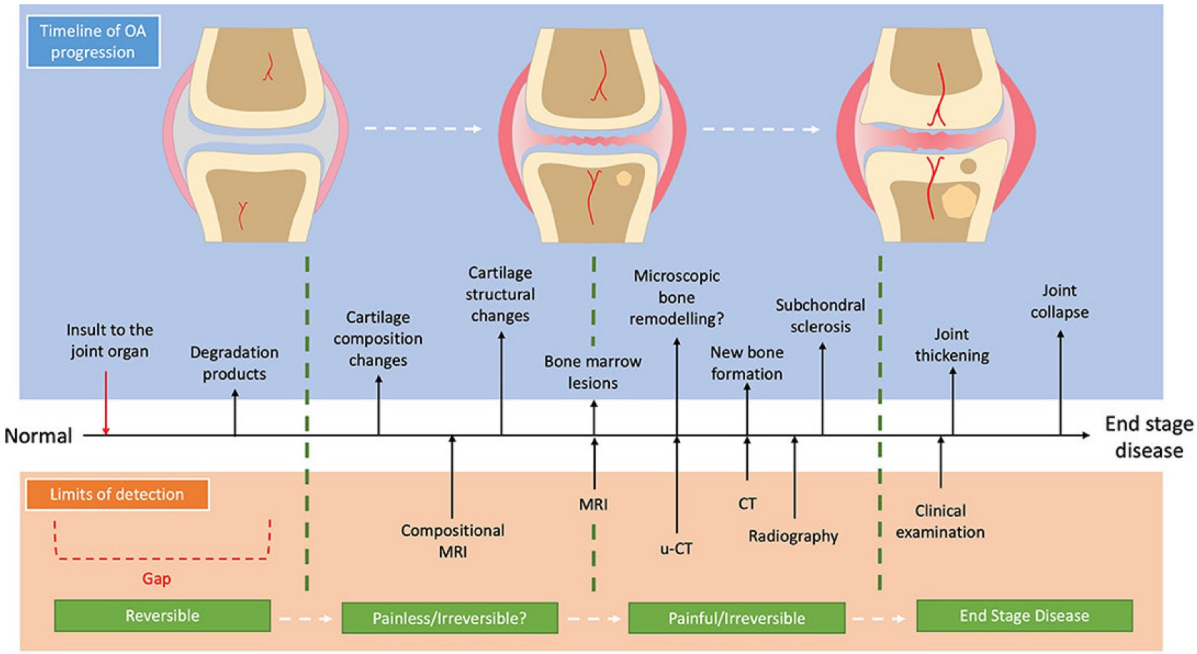

Figure 10 Schematic representation of the diseases stages next to the present limits of advanced diagnostic imaging methods. [2]

Concluding it can be said, that up to the present state of knowledge, the definite diagnosis of canine OA prior to the occurrence of irreversible changes cannot be made. Consequently, the disease remains considered as non-curative. But certain diagnostic tools give a promising outlook for the breakthrough in closing the gap between the occurrence of irreversible changes and the time of the earliest possible diagnosis, if further research and improvements are made.

8 Discussion

As already mentioned in the results, the outcome of this systematic literature review has revealed that to date, the diagnosis of canine OA prior to the occurrence of irreversible changes remains impossible, and therefore the disease still has to be characterized as non-curable. There are existing diagnostic imaging tools, including radiography and CT, that can definitely provide an accurate diagnosis in the case of OA. On the downside, those tools have a very limited sensitivity regarding early canine OA diagnostics. Other already existing advanced imaging methods, such as micro-CT, MRI, gamma scintigraphy and PET, show promising potentials if further worked on.

Many of the new findings regarding early OA detection originate from researches in human medicine, such as the identification of some of the early OA biomarkers via nuclear medicine, and are assumed to be true for veterinary medicine. In most of the cases, only a few studies are made concerning their use in animals to support those findings. Investigations based on higher numbers of animals, different primary causes of OA, breeds, genders and ages could help to confirm their occurrence in the common canine population. Apart from that, it is necessary to work on technological weaknesses, for example the excess amounts of radiation in micro-CT imaging, to be able to implement some tools in the everyday practice. Miscellaneous limitations, regarding costs, availability and specific regulations applying to some methods, have to be eliminated to enable their widespread use. The introduction of those relatively unusual imaging methods to everyday practice is essential to further explore their effectivity on the one hand, on the other hand, this could contribute to a whole new strategy. This new approach is based on the hypothesis, that the already existing imaging methods are able to detect reversible changes of OA already, but we are simply unaware of those changes and their combinations. Consequently, rather than improving technologies and searching for new methods, the already known ones have to be focused on. In addition, the introduction of artificial intelligences (AI) for the evaluation of results could help to identify further early biomarkers, their combinations and erase false negative cases. Assuming that through the widespread use of several imaging methods collective databases are created, AIs could evaluate and compare this data and make a diagnosis based on this information. Signs that would be missed by the sole evaluation of the human eye are less likely to impossible to be missed by this assessment approach.

Looking into the future, there is more than one possible solution that could finally lead to the breakthrough in the detection of early canine OA prior to the occurrence of irreversible changes. One is to find out about new technologies that can depict what has been invisible until now. Another one is to work on the already existing imaging methods. Either through improvement of their technologies, thus decreasing their limitations, or through scientific research to find out about their particular, possibly unknown features. Furthermore, additional technologies could be introduced for the interpretation and evaluation of results, as a way to eliminate human weaknesses regarding the comparison and connection finding in a broad spectrum of data. The next important task is to find the most target-orientated solution to solve the present complications and thereby close the gap between the earliest detection possible and the onset of irreversible changes.

9 Summary

In this systematic literature review, present to futuristic diagnostic tools were discussed, regarding their ability of being able to diagnose canine OA before irreversible alterations start to develop. Thus, enabling a therapeutic approach with the goal to completely cure the affected animals.

As a result, two major groups of advanced imaging methods were identified. The first group includes the ones being able to provide a definite diagnosis of OA at some point of the disease, but with very limited capability to enable the final goal of early canine OA detection. Representatives of this group are the ionizing radiation-based radiography and CT. The second group contains imaging methods characterized by a high potential for early OA detection. This group can again be divided into two subgroups. One is based on the common structural imaging, such as micro-CT and MRI. The other one consists of functional imaging-based technologies, like gamma scintigraphy and PET. The representatives of the second major group cannot yet diagnose OA prior to the occurrence of irreversible changes, but they show a promising potential if their technologies are improved and the knowledge regarding those tools is expanded through research concerning veterinary medicine.

A second look at the result has revealed, that the problem can be approached in various ways. Goal-leading paths could be the development of new technologies, the improvement of already existing ones, through technological or scientific based upgrades, or the more futuristic approach of introducing AIs for evaluation and comparison of results from databases.

Considering the above-mentioned and looking into the future, the major task now is to find and work on the right approach or combination of approaches and diagnostic tools to enable the diagnosis of canine OA prior to the occurrence of irreversible changes as close to the time as possible.

To come back to the initial objective of this review, the results of this research are negative regarding the central question if canine OA can be diagnosed before irreversible alterations of the joint start to develop. Up to the present state of knowledge, it is impossible to make a definite OA diagnosis prior to the occurrence of irreversible changes. Meaning that the gap between the onset of irreversible changes and the earliest diagnosis possible could not be closed yet. Consequently, the disease remains considered as non-curative regarding its therapy.

10 Bibliography

1. Shell L, Harasen G (2021) Degenerative Joint Disease (Canine). VIN.com
2. Jones GMC, Pitsillides AA, Meeson RL (2022) Moving Beyond the Limits of Detection: The Past, the Present, and the Future of Diagnostic Imaging in Canine Osteoarthritis. Front Vet Sci 9:
3. Johnston SA (2005) Osteoarthritis-What is it ? VIN.com
4. Johnston SA (2015) Multilevel Pain Control for Osteoarthritis. VIN.com
5. Bland SD (2015) Canine osteoarthritis and treatments: a review. Vet Sci Dev 5:. https://doi.org/10.4081/vsd.2015.5931
6. Dunkin MA (2022) Testing for Osteoarthritis| Arthritis Foundation. https://www.arthritis.org/diseases/more-about/tests-for-osteoarthritis. Accessed 7 Sep 2023
7. Mauterer J (2022) Athrocentesis Made Easy. VIN.com
8. Roemer FW, Demehri S, Omoumi P, Link TM, Kijowski R, Saarakkala S (2020) State of the Art: Imaging of Osteoarthritis—Revisited 2020. https://pubs.rsna.org/doi/epdf/10.1148/radiol.2020192498. Accessed 13 Jul 2023
9. Magnetic Resonance Imaging (MRI). In: Natl. Inst. Biomed. Imaging Bioeng. https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri. Accessed 9 Sep 2023
10. Greco A, Meomartino L, Gnudi G, Brunetti A, Di Giancamillo M (2023) Imaging techniques in veterinary medicine. Part II: Computed tomography, magnetic resonance imaging, nuclear medicine. Eur J Radiol Open 10:100467. https://doi.org/10.1016/j.ejro.2022.100467
11. Sobal G, Pagitz M, Velusamy K, Koisk S, Sinzinger H Successful imaging of osteoarthritis with 99mTc radiolabeled chondroitin sulfate (CS) in dogs | Journal of Nuclear Medicine. https://jnm.snmjournals.org/content/54/supplement_2/251. Accessed 13 Sep 2023
12. Frye CW (2018) Joint-Modifying Agents and Osteoarthritis - Where is the Evidence ? VIN.com
13. Brooks W (2022) Medications for Degenerative Arthritis in Dogs and Cats. VIN.com
14. Grubb T (2018) Gabapentin and Amantadine for Chronic Pain: Is Your Dose Right? In: Todays Vet. Pract. https://todaysveterinarypractice.com/pain_management/gabapentin-and-amantadine-for-chronic-pain/. Accessed 27 Jul 2023
15. Baker-Meuten A, Wendland T, Shamir SK, Hess AM, Duerr FM (2020) Evaluation of acupuncture for the treatment of pain associated with naturally-occurring osteoarthritis in dogs: a prospective, randomized, placebo-controlled, blinded clinical trial. BMC Vet Res 16:357. https://doi.org/10.1186/s12917-020-02567-1
16. Aulakh KS, Lopez MJ, Hudson C, Gaschen L, Fabiani M, Beale B, Andrews FM, Liu C-C, Lattimer J (2021) Prospective Clinical Evaluation of Intra-Articular Injection of Tin-117m (117mSn) Radiosynoviorthesis Agent for Management of Naturally Occurring Elbow Osteoarthritis in Dogs: A Pilot Study. Vet Med Res Rep 12:117–128. https://doi.org/10.2147/VMRR.S295309
17. Donecker J, Fabiani M, Gaschen L, Aulakh KS (2021) Treatment response in dogs with naturally occurring grade 3 elbow osteoarthritis following intra-articular injection of 117mSn (tin) colloid. PLOS ONE 16:e0254613. https://doi.org/10.1371/journal.pone.0254613

18. Synovetin OA® | Introducing Synovetin OA® | Canine Elbow Osteoarthritis Management. https://www.synovetin.com/. Accessed 25 Sep 2023
19. Donecker J, Lattimer JC, Gaschen L, Aulakh KS (2021) Safety and Clinical Response Following a Repeat Intraarticular Injection of Tin-117m (117mSn) Colloid in Dogs with Elbow Osteoarthritis. Vet Med Res Rep 12:325–335. https://doi.org/10.2147/VMRR.S345144

Thesis progress report for veterinary students

Name of student: .....Hana..Sophie..Müller.....

Neptun code of the student: ...CIN5XU.....

Name and title of the supervisor: .Dr...Anna....Szalai.,DVM.,PhD.....

Department:...Pathology.....

Thesis title: ..Osteoarthritis..in..dogs.-..Early..diagnosis...of..canine....
.osteoarthritis...prior...to..the..occurrence..of...irreversible.....
.changes.....

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	11	16	Overview of topic	
2.	2023	01	11	Checking of available literature	
3.	2023	02	08	Introduction	
4.	2023	03	22	Consultation on literature	
5.	2023	05	10	Consultation on topic + address	

Grade achieved at the end of the first semester: .....fines...(5).....

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	06	21	Overview of literature review part 1	
2.	2023	08	23	— " — part 2	
3.	2023	09	13	Correction part 1	
4.	2023	10	11	— " — part 2	

5.	2023	10	25	Final review, abstract	

Grade achieved at the end of the second semester: .....jeles (5).....

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in..... .....

I hereby confirm that I am familiar with the content of the thesis entitled

Osteoarthritis in dogs - Early diagnosis of canine osteoarthritis prior to the occurrence of irreversible changes written by Marie Sophie Müller

(student name) which I deem suitable for submission and defence.

Date: Budapest, 14 day 11 month 2023 year

Dr. Anna Szilasi

..... Supervisor name and signature

Department of Pathology

..... Department