Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 932–939

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Antigen-induced arthritis of the temporomandibular joint via repeated injections of bovine serum albumin in domestic pigs

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ARTICLE INFO

Article history:
Paper received 19 December 2018
Accepted 1 March 2019
Available online 7 March 2019

Keywords:
Rheumatoid arthritis
Temporomandibular joint
Antigen-induced arthritis
Large animal model

ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease and the temporomandibular joint (TMJ) is affected in up to 50%, resulting in pain, limited mouth opening and dental malocclusion. The outcome of conservative and surgical therapies is unsatisfying in many cases. The purpose of this study was to establish a large animal model of antigen-induced arthritis (AIA) of the TMJ that enables the investigation of the pathogenesis of RA and the evaluation of new therapies. In five domestic pigs, systemic immunization was performed via consecutive intramuscular injections of bovine serum albumin (BSA). Then, AIA was induced via the application of BSA into the TMJ. Injection with saline served as the control. After ten weeks, the joints and adjacent tissues were harvested for histological analysis and cytokine quantification. The changes observed in the AIA specimens included severe synovial inflammation, cartilage-specific glycosaminoglycan content loss, and cartilage surface and discus alterations as well as the formation of chondrocyte clusters. Protein analyses of the synovia showed enhanced levels of IL-1β, IL-6, TNFα and VEGF. A porcine model of immunologic arthritis of the TMJ was successfully established. This model may be used in future studies to investigate the underlying pathogenesis of RA and new therapeutic strategies.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that mainly affects the synovial tissue, cartilage and underlying bone tissue. The inflammation, or osteoarthritis (OA), leads to the progressive remodeling and destruction of joints as well as pain, dysfunction and reduced health-related quality of life (Johnson and Hunter, 2014). RA can affect one or various joints and may even occur systemically in the context of inflammatory syndromes (van der Kraan, 2013). RA has an incidence of 0.5–1%, with an apparent reduction from north to south (in the northern hemisphere) and from urban to rural areas (Smolen et al., 2016). The temporomandibular joint (TMJ) is affected in 10–30% of patients with newly diagnosed RA (Chin Jen Sem et al., 2017; Aceves-Avila et al., 2013). Radiological evaluations in patients diagnosed with RA show that degenerative bone changes at the TMJ are present in 90% of patients and that there is a greater tendency to develop degenerative changes in asymptomatic individuals (Cordeiro et al., 2016). Patients suffering from osteoarthritis of the hand seem to be highly correlated with patients with TMJ disorders. In one study, while self-reported symptoms were present in 44% of patients, clinical TMJ-related examination findings were observed in 93% of the cohort (Abrahamsson et al., 2017). Osteoarthritis of the TMJ may lead to substantial joint and muscle pain, limited mouth opening, joint sounds such as clicking and crepitus, dental malocclusion and reduced health-related quality of life (Chantaracherd et al., 2015; Wang et al., 2015). The most prevalent radiographic findings are joint effusion, increased contrast enhancement, flattening of the condyle, cysts, osteophytes and ankyloses (Muller et al., 2009; Cevidanes et al., 2014; Comert Kilic et al., 2015). Early diagnosis and the initiation of therapy are important to prevent progressive destruction and remodeling of the joint. In particular, children with juvenile arthritis of the TMJ can suffer from growth disturbances of the mandible that lead to facial asymmetry and severe malocclusion (Koos et al., 2014a,b).

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https://doi.org/10.1016/j.jcms.2019.03.001
1010-5182/

The treatment of RA of the TMJ can be divided into conservative and surgical procedures. Initially, a conservative approach such as anti-inflammatory and immunomodulatory medications (Smolen et al., 2014), local drug application (Stoll et al., 2013), mechanical and orthodontic measures (Kuroda et al., 2012) and supportive lifestyle modifications are recommended. If surgical procedures are necessary, they can be carried out with minimally invasive or open surgical procedures, depending on the extent of RA (Sidebottom and Salha, 2013). Minimally invasive approaches include arthroscopic lysis and lavage, drug instillations and condylar shaving (Gonzalez-Garcia, 2015). When open surgery is needed, there are several techniques used for the shaping, reconstruction and regaining of joint function (O'Connor et al., 2017). Total prosthetic joint replacement is accepted as an ultimate ratio treatment in the reconstruction of a severely altered TMJ (O'Connor et al., 2016). Although relevant advantages are apparent in introducing biologic preparations that interact with specific signaling pathways, the side effects, therapeutic outcomes and disease progression associated with treatment are unsatisfying in many cases (Vidqvist et al., 2013). To gain a better understanding of the pathogenesis of RA and to investigate new and innovative therapeutic strategies, animal models of immunological arthritis are needed. The induction of arthritis has been established successfully by the genetic manipulation of collagen, cytokines, matrix metalloproteinases and small leucine-rich repeat proteoglycan genes (Ghassemi Nejad et al., 2017) as well as proinflammatory intraarticular injections (Chaves et al., 2011; Ghassemi-Nejad et al., 2011). Furthermore, a multitude of surgical models, including different techniques of disc perforation, disc resection and condylar surface impairment have been introduced in different species and models using mechanical overload protocols (Xu et al., 2009; Embree et al., 2015). The best way to simulate the pathomechanism of immunological arthritis is via antigen-induced arthritis (AIA) of the TMJ. The underlying principle of this approach is systematic immunization via repeated injections of an antigen followed by intraarticular administration, resulting in consecutive immunological osteoarthritis of the TMJ. In small animals, AIA has been established utilizing different types of proteins, such as ovalbumin or bovine serum albumin (Kuseler et al., 2004, Rafayelyan et al., 2015a,b). Large-species animal models investigating AIA in the TMJ have not yet been developed but are of great interest because the size, anatomy and mechanical loading in large animals are comparable to those in humans. This approach allows a more translational simulation of the disease pathogenesis and, as a future goal, the evaluation of therapeutic interventions (Kaduk and Koppe, 2007). The pig is the most suitable species based on the morphology of the TMJ as well as the omnivore nutritional status and manner of mastication of the pig, which are comparable to those in humans (Strom et al., 1986; Fernandez et al., 2013). The purpose of this study was to develop reliable and predictable antigen-induced arthritis of the TMJ in a large animal model and quantify the initial inflammatory reaction.

2. Material and methods

2.1. Experimental animals

Animal experiments were conducted according to the European Animal Welfare Legislation, the European Directive 2010/63/EU, and the experiments were conducted in compliance with the ARRIVE guidelines. The study protocol was approved by the Directorate of Food-Chain and Animal Healthcare, Hungary (Approval No. PEI/001/961-2/2013). The study included ten skeletally mature domestic pigs (*Sus scrofa domesticus*) with an average age of 6 months and an average weight of 95 kg. All animals were kept under conventional conditions, with a circadian day and night rhythm and an open enclosure of 6 m^2 at an ambient room temperature of 18 ± 1 °C. The pigs received standardized pig fodder and water *ad libitum*. The animals were identified by ear markers and randomly divided into an immunization group and a non-immunization group of five specimens each.

2.2. Systemic immunization

The animals were sedated before application of the immunization procedure via the subcutaneous injection of 10 mg/kg bodyweight (mg/kg bw) ketamine (Ketavet®, Ratiopharm, Ulm, Germany). Vital signs were monitored by a veterinarian. In five pigs, the immunization was performed by repeated injections of bovine serum albumin (BSA, Fraction V, Sigma Aldrich, St. Louis, USA). Therefore, BSA was eluted in physiological saline to a concentration of 10 mg/ml and sterile filtered, with a pore size of 0.2 μm. The BSA solution was injected intramuscularly in the hip, with a dosage of 8 mg/kg bw five times total, at intervals of one week per injection. The control group was injected with the same volume of physiological saline at the same hip location and time points (Fig. 1).

2.3. Intraarticular injection

AIA was triggered in one TMJ by repeated injections of BSA, beginning one week after systemic immunization. The animals were sedated as described above. BSA was eluted in physiological saline to a concentration of 5 mg/ml and filtered using a sterile filter with a pore size of 0.2 μm. The BSA solution was injected into the left TMJ, with a dosage of 2 mg/kg bw five times total, at intervals of one week per injection. As a control, the same volume of physiological saline was administered intraarticularly on the right side (Fig. 1). For access to the TMJ, a needle (diameter 18 gauge, length 5 cm) was inserted at the lower-dorsal edge of the zygomatic arch

	systemic immunization (i.m.)					intraarticular injection (i.a.)					
week	0	1	2	3	4	5	6	7	8	9	10
treatment group (5 pigs)	BSA	BSA	BSA	BSA	BSA	BSA left	BSA left	BSA left	BSA left	BSA left	euth
						saline right	saline right	saline right	saline right	saline right	euth
control group (5 pigs)	saline	saline	saline	saline	saline	BSA left	BSA left	BSA left	BSA left	BSA left	euth
						saline right	saline right	saline right	saline right	saline right	euth

Fig. 1. Timeline of the injections for systemic intramuscular (i.m.) immunization and the intraarticular (i.a.) injections. The administration-protocols of bovine serum albumin (BSA) and physiological saline in the four treatment groups are demonstrated. Euthanasia (euth) and the harvesting of the TMJs for histological analysis are performed after 10 weeks.

at a distance 6 cm below the tragus. The entry direction was perpendicular to the surface of the skin (Fig. 2). The intraarticular location of the needle tip was verified by the aspiration of synovial fluid.

2.4. Blood analysis

To evaluate the impact of immunization and antigen-induced arthritis on a systemic level, blood samples were collected by puncture of the jugular vein before the first immunization and after the fifth intraarticular injection. At the Institute of Clinical Chemistry at the University Hospital Schleswig–Holstein, Campus Kiel, the quantification of relevant inflammatory parameters such as white blood cells, C-reactive protein, and immunoglobulin type M and type G was performed following the accredited protocols.

2.5. Histological analysis

After ten weeks, euthanasia was performed via intramuscular injection of Azaperone® (1 mg/kg) and Midazolam® (1 mg/kg) as well as a consecutive intravenous overdose of 20% pentobarbital. The TMJs and the adjacent tissues were dissected and halved lengthwise with a diamond-coated saw (Cut-grinder primus Diamant, Walter Messner GmbH, Oststeinbeck, Germany). One half of each sample was deep frozen for protein analysis, while the other half was fixed in 4% formalin for 14 days. Then, the specimens were decalcified in 0.5 M EDTA (pH 7.4) and embedded in paraffin. Sections 6 μm thick were cut with a sliding microtome (HM 430, Microm International, Walldorf, Germany) and routinely stained with hematoxylin-eosin (HE). Safranin-O staining was carried out for 6 min using a 0.1% aqueous solution at pH 3. All specimens were examined by light microscopy (Axio Oberserver.Z1 and Axio Cam and Axio Vision, Carl Zeiss Mikroskopie, Jena, Germany). To classify the arthritis changes, the synovial membrane, discus, cartilage and condyle were analyzed. The thickness of the synovial membrane was measured in the upper and lower compartments at three positions each, and the modified Goldberg score was utilized (Ohashi et al., 1996). The discus thickness was measured at the thinnest part, as the disintegration of the fibrous discus is a symptom of TMJ arthritis that may lead to perforation over time. Additionally, scoring of the microscopic signs of discus alterations was conducted. In the cartilage, the content of proteoglycans was evaluated using the scores of Safranin-O staining (Rosenberg, 1971). The morphological changes of the condyle were assessed by the ICRS Visual Histological Assessment Scale (Mainil-Varlet et al., 2003).

Fig. 2. Illustration of intraarticular injection on an anatomical model. The intraarticular injection was performed at the lower-dorsal edge of the zygomatic arch 6 cm from the tragus. The direction of the needle is perpendicular to the surface of the skin.

2.6. Protein analysis of the synovium and cartilage

Frozen samples were homogenized with an agate stone mortar using liquid nitrogen (−196 °C), and IL-1β, IL-6, TNFα, and VEGF concentrations in the obtained homogenates were analyzed by a Luminex assay (Qiagen Multiplex Analyzer LiquiChip 200, BaneBio, Buckeystown, USA) according to standard protocols. For the detection of IL-1β, IL-6, TNFα, and VEGF contents, the Milliplex human cytokine multiplex immunoassay kit (BaneBio, Buckeystown, USA) was used. The results were assessed for the overall protein content of the respective samples.

2.7. Statistics

All proportional scaled data were collected and presented as the means, standard errors of the mean and 95% confidence intervals (95% CIs). The data sets were tested for normal distribution and homogeneous variance. The data sets were analyzed using two-way analysis of variance (ANOVA), followed by Tukey's HSD post hoc test (SPSS Statistics 20.0, International Business Machines Corporation, Armonk, USA). The significance level was set to a p value of 0.05. Ordinal scaled data were described as the median and frequency of distribution.

3. Results

3.1. Baseline results

The systematic immunizations and intraarticular injections were well tolerated by all animals. Clinical examinations revealed no signs of local inflammation, allergic reactions or toxic side effects. The ability of the pigs to eat and chew as well as the range of movement of the mandible appeared unaffected, and the body weights remained stable. The data of all animals were included in the results.

3.2. Blood analysis

The quantification of the white blood cells showed that there were 20.15 cells/nl (95% CI 18.63–21.67) before injection, 21.54 cells/nl (95% CI 19.61–21.47) after immunization and 19.98 cells/nl (95% CI 19.34–20.62) after saline injections. The C-reactive protein content was less than the lower detection limit (<0.9 mg/l) in all animals with both injection regimens. The immunoglobulin type M content was 1.95 mg/ml (95% CI 1.61–2.28) at baseline, 1.69 mg/ml (95% CI 1.36–2.01) in the immunized pigs and 1.56 mg/ml (95% CI 1.24–1.94) in the non-immunized animals. The immunoglobulin type G content was 8.28 mg/ml (95% CI 7.91–8.64) at baseline, 8.53 mg/ml (95% CI 8.04–9.02) after immunization and 9.38 mg/ml (95% CI 8.88–9.88) in the nonimmunized pigs. The immunization procedure did not show any significant impact on the systemic inflammation markers.

3.3. Synovial and discus changes

The synovial membrane in the test group showed clear histological signs of inflammation, primarily hyperplasia, and a villous and rough surface as well as the infusion of leucocytes (Fig. 3). The thickness of the synovia was significantly increased in the animals

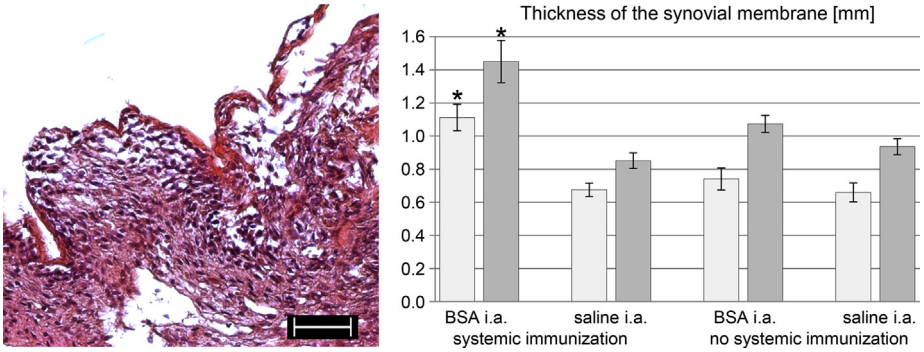

Fig. 3. Morphologic changes in the synovial membrane from the TMJ of pigs with antigen-induced arthritis. Left, hematoxylin-eosin staining of a representative specimen shows synovial hypertrophy and leucocyte infiltration. The scale bar is 50 μm. The graph on the right side demonstrates the thickness of the synovial membrane in all treatment groups in the upper (light gray) and the lower compartment (dark gray). The synovia are significantly thicker (marked with an asterisk) in the antigen-induced arthritis group in both compartments.

that received systemic immunization and intraarticular BSA injections (Fig. 3). In accordance with these findings, the highest modified Goldberg scores were found in the specimens treated with the AIA protocol (median 2, other treatment groups median 1). Protein analysis of the synovium showed significantly increased levels of IL-1β (55.74 pg/mg, 95% CI 52.23–59.25), TNFα (29.78 pg/mg, 95% CI 27.77–31.79) and VEGF (4.72 μg/mg, 95% 4.52–4.92) in the AIA specimens. The IL-6 level was increased (41.45 pg/mg, 95% CI 36.57–46.34) by systemic immunization and intraarticular BSA injections but not to a significant extent compared to that of the control groups (Fig. 4). The thickness of the discus was 2.09 mm (95% CI 1.94–2.23) in the animals treated with the AIA protocol and was not different from that of the other treatment groups (2.08 mm, 95% CI 1.93–2.23; 2.15 mm, 95% CI 2.09–2.21; 2.15 mm, 95% CI 2.05–2.25). Histologically, the inner structure of the discus appeared to be unaffected, while the surface of the discus in the antigen-induced arthritis group was roughened in every specimen (Fig. 5).

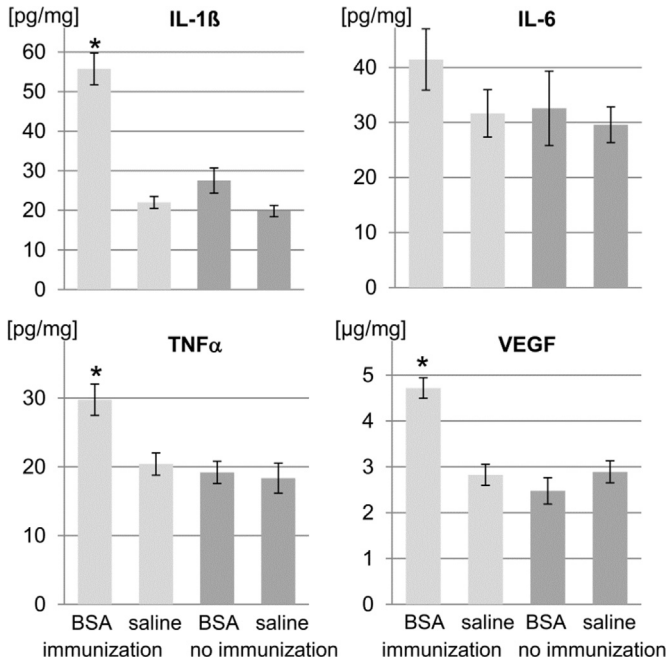

Fig. 4. Results of the protein analysis of the TMJ synovium by Luminex assay. Significantly increased levels (marked with an asterisk) of interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα) and vascular endothelial growth factor (VEGF) occur in the antigen-induced arthritis specimens. The interleukin-6 (IL-6) level is increased by systemic immunization and intraarticular BSA injections, but not to a significant extent. The protein levels in the control groups are in a homogenous range.

3.4. Cartilage and condylar changes

The assessment of the condylar cartilage did not indicate any divergence among the treatment groups concerning subchondral bone, chondral mineralization, cellular distribution or the extracellular matrix. However, the cartilage surface showed a higher number of affected surfaces in the AIA specimens (median 0 in contrast to median 1 in all other groups). Additionally, in the AIA specimens, morphological changes, such as cystic alterations, with the consecutive displacement of adjacent chondrocytes were apparent (Fig. 6). The Luminex assay quantifying Il-1β, IL-6, TNFα and VEGF was feasible only in a few specimens, as the amount of cartilage tissue of the halved temporomandibular condyles was not sufficient. Therefore, no valid results from the protein analysis were available. There was a relevant decrease in the proteoglycan content in the specimens with antigen-induced arthritis (- -) and a slight decrease in the nonimmunized animals with intraarticular BSA injections (-) compared to that of the animals with intraarticular saline application (0), especially in the superficial layers (Fig. 7).

4. Discussion

In this study, we developed a porcine model of immunologic arthritis. To the best of our knowledge, this is the first large animal model for rheumatic joint disease of the TMJ. In the literature, a multitude of protocols using various antigens, dosages, frequencies, species and joints have been reported previously. Bovine serum albumin is a xenogeneic protein that has been established for a long time, has been widely investigated and leads to a reliable immunologic response if applied repetitively (Jones et al., 2018). The protocol of this study for the systemic immunization and the intraarticular injection has been obtained from Silva Quinteiro et al. who induced immunological arthritis in the TMJ of rats and Rafayelyan et al. who investigated AIA in the TMJ in rabbits (Silva Quinteiro et al., 2014; Rafayelyan et al., 2015a,b). In addition to the two previously mentioned studies, the protocol has been further modified by the descriptions of Ohashi et al. and Lippross et al. that induced immunologic arthritis in the knee of beagle-dogs and domestic pigs (Ohashi et al., 1996; Lippross et al., 2011).

In accordance with published reports on the induction of synovitis in the TMJ of small animal models (Kristensen et al., 2008,

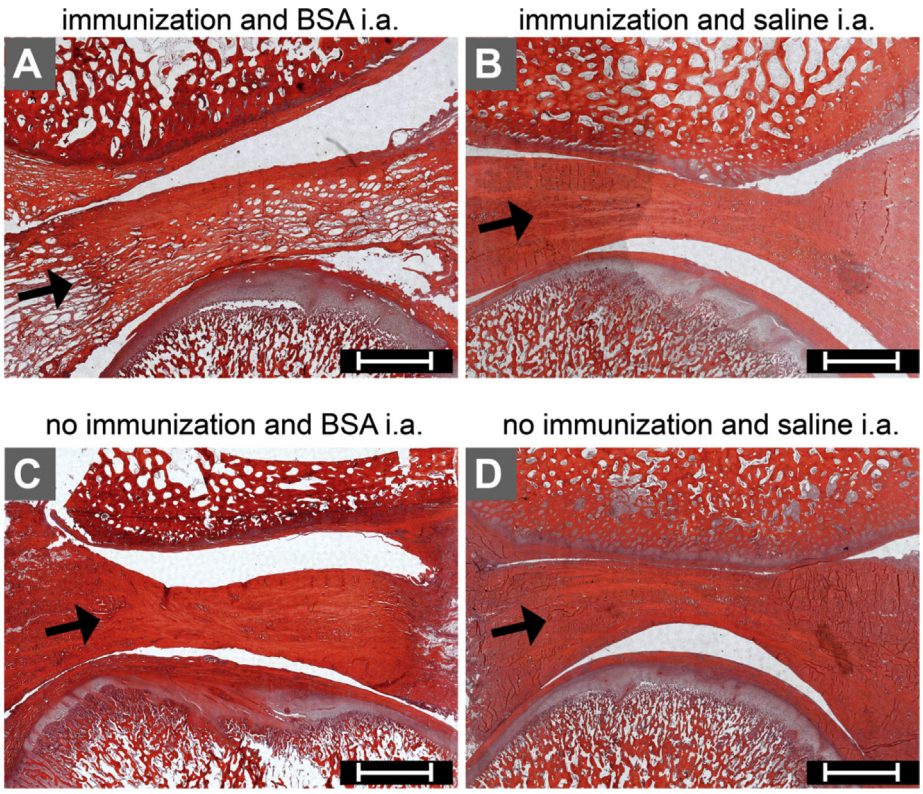

Fig. 5. Hematoxylin-eosin staining of the temporomandibular joints of all treatment groups. The upper compartment is bounded by the temporal fossa and the upper surface of the discus, which is marked with an arrow. The lower compartment includes the mandibular condyle and the bottom surface of the discus. The discus with antigen-induced arthritis exhibits a normal thickness but roughness on the surface, which is not present in the other groups. The scale bar is 2000 μm.

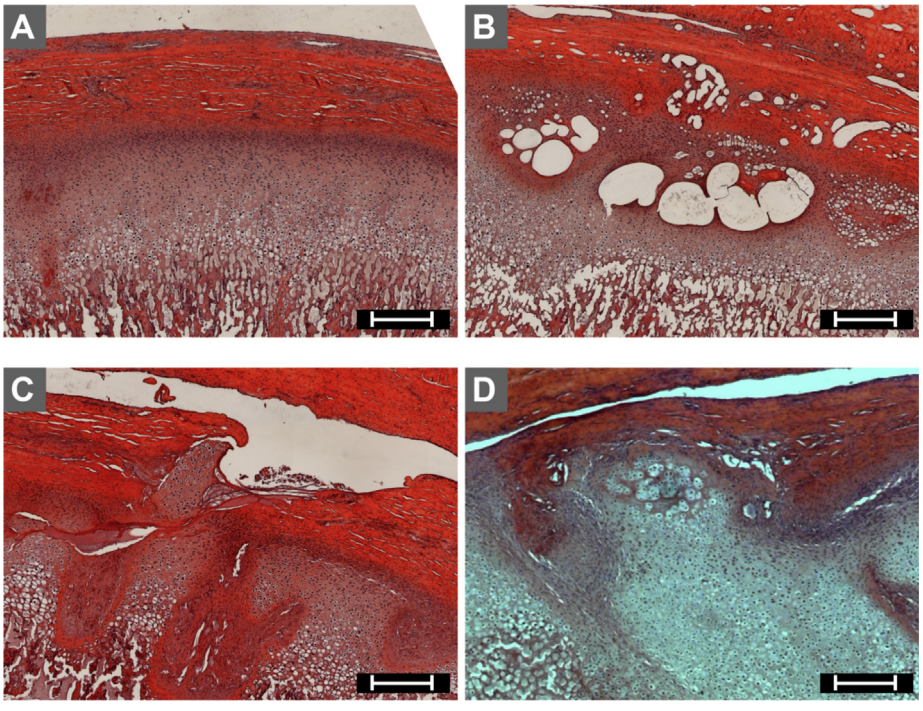

Fig. 6. Hematoxylin-eosin staining of representative morphological changes of the condylar cartilage. The unaffected cartilage consists of a typical hyaline morphology with a homogenous extracellular matrix and cell distribution (A). Representative morphological changes in affected specimens are cystic lesions with consecutive displacement of the chondrocytes (B), surface disintegration (C) and the formation of cell clusters (D). The scale bar is 500 μm.

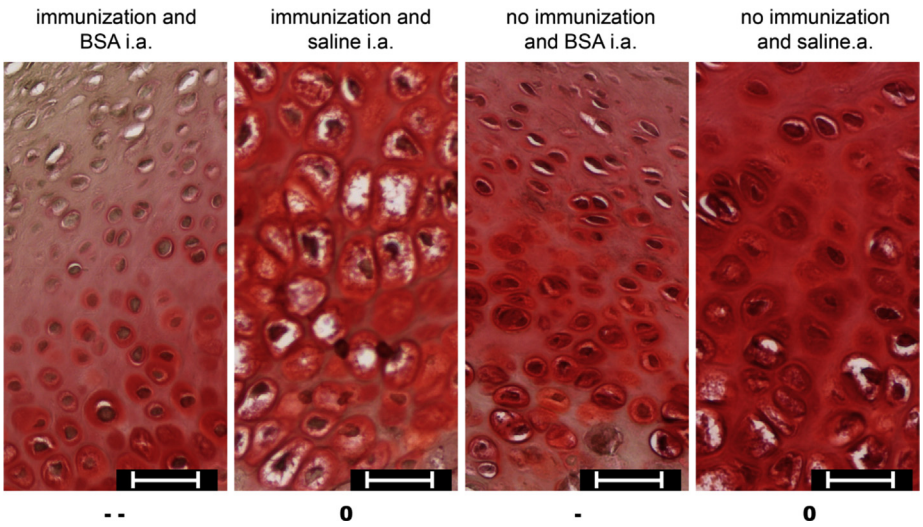

Fig. 7. Safranin-O staining of the condylar cartilage of all treatment groups. The semiquantitative evaluation of the proteoglycan content shows a relevant decrease in the antigen-induced arthritis (- -) specimens and a slight decrease in the nonimmunized animals with intraarticular BSA injections (-) compared to the animals with intraarticular saline application (0). The scale bar is 50 μm.

Rafayelyan et al., 2015a,b), we conclude that our model can serve as a tool to analyze early inflammatory arthritis. However, from a translational perspective, it must be taken into account that AIA did not lead to any measurable systemic inflammatory reactions, which deviates from findings in humans suffering from rheumatoid arthritis (Cevidanes et al., 2014). Especially raised levels of serum CRP seem to be associated with progression of TMJ bone loss (Nordahl et al., 2001).

We chose the porcine model for investigating AIA because pig TMJs are more comparable to human TMJs than those of various small animals that have been used in well-established models. The anatomy and manner of mastication of pigs have previously been compared to those of humans and were shown to be similar and thus translational (Herring et al., 2002).

The changes observed in the AIA specimens included severe synovial inflammation, cartilage-specific glycosaminoglycan content loss, and cartilage surface and discus alterations as well as the formation of chondrocyte clusters. Similar findings have been reported in other animal studies, with chondral damage generally considered a characteristic feature of immunologic arthritis (Silva Quinteiro et al., 2014, Rafayelyan et al., 2015a,b).

Consistent with the analysis of morphological changes, protein analyses of the synovia showed enhanced levels of the inflammatory markers IL-1β, IL-6, TNFα and VEGF. There is ongoing debate regarding which molecular marker is the most important in the detection and quantification of osteoarthritis changes. VEGF plays a key role in the hypervascularization of inflamed tissue and represents an early marker of arthritis and synovitis (Pufe et al., 2001; Fay et al., 2006). VEGF levels in the plasma and synovial fluid are considered suitable to monitor the severity of osteoarthritis (Saetan et al., 2014). The inhibition of the effects of VEGF is a recently emerging concept in the treatment of inflammation (Abdel-Maged et al., 2018).

In contrast, the activation of the cytokine cascade downstream of TNFα is a mechanism that has long been recognized. This concept has led to *in vitro* and *in vivo* investigations with the aim of specifically inhibiting these cytokines (Ohtani et al., 2012). Various biological agents have been introduced and are currently utilized in clinical trials (Luchetti et al., 2017). As a consequence, IL-1β, IL-6 and TNFα were a major focus of our evaluation of the porcine arthritis model. In accordance with the findings in rats by Pohlers et al. (2005), we demonstrated increased levels of all markers, including TNF. However, the pathogenesis of osteoarthritis seems to be more complex and is not yet fully understood. A multitude of cytokines play a role in different stages of RA and participate in sophisticated interactions (Siebert et al., 2015). Future studies may focus on other factors and pathways to gain a deeper understanding of the development of RA.

Unfortunately, due to the small amount of condylar cartilage, protein quantification was possible only in a few specimens, resulting in a lack of quantification. A previous study that used a very similar protocol to induce AIA and performed protein quantification with the same method found that the overall concentration of inflammatory proteins was lower in cartilage tissue than that in synovia; however, in the AIA-treated specimens, the increase did show a comparable adjustment (Lippross et al., 2011). These findings are in accordance with those of other investigators, which demonstrated the upregulation of cytokine production in chondrocytes under arthritic conditions (Hoff et al., 2013).

The relatively low number of animals included in the study weakens the results but is a common problem in large animal models because of ethical considerations and administrative requirements. Nevertheless, we believe that the consistency of the results with regard to the induction of arthritis outweighs this weakness. Therefore, we consider the number of animals used to be appropriate for drawing the conclusions reported.

5. Conclusion

In summary, we established a novel large animal model of AIA of the temporomandibular joint in which we documented microscopic synovial and cartilage changes and an increase in the levels of inflammatory mediators in synovial tissue. Future studies using this pig model can evaluate the effectiveness of both local and systemic therapeutic interventions.

Role of the funding sources

This work was supported by the Medical Faculty of the University of Kiel [grant no. F348020].

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank Gaby Neßenius for her technical expertise and excellent support of this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.03.001.

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