Does Hypoxia-Reperfusion Injury Occur in Osteoarthritis of the Temporomandibular Joint?

Lukas M. Vos, DMD
Research Assistant
Department of Oral and Maxillofacial Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

James J. R. Huddleston Slater, DMD, PhD
Senior Researcher
Department of Oral and Maxillofacial Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Martha K. Leijsma, MD
Senior Researcher
Department of Rheumatology and Clinical Immunology
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Boudewijn Stegenga, DMD, PhD
Professor
Department of Oral and Maxillofacial Surgery
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Correspondence to:
Dr Lukas M. Vos
Hanzeplein 1, PO Box 30 001
9700 RB Groningen
The Netherlands
Fax : +31 (0)50 361 11 36
Email: l.m.vos@umcg.nl

Aims: *To determine the available evidence in the literature for whether hypoxia-reperfusion injury plays a role in the pathogenesis of joint diseases in general and of osteoarthritis (OA) of the temporomandibular joint (TMJ) in particular.* ***Methods:*** *The electronic databases CENTRAL, PubMed, and EMBASE were systematically searched. The search strategy combined thesaurus terms "reperfusion injury" and "joints" and excluded "tourniquet," which possibly induces iatrogenic reperfusion injury. Inclusion and exclusion criteria were applied, data were extracted, and quality was assessed.* ***Results:*** *Four studies could be included, investigating four different aspects of the hypoxia-reperfusion mechanism in joints. All studies investigated several arthritides in the knee or shoulder joint and were observational studies, except for one section of one of the studies, which was a randomized controlled trial. These studies do not provide any evidence to support or reject the hypothesis that hypoxia reperfusion occurs in TMJ OA. Positive but weak evidence is provided to support the hypothesis that hypoxia-reperfusion injury occurs in OA of the knee joint. Furthermore, some results of the included studies suggest differences between OA and other types of arthritis in relation to the hypoxia-reperfusion mechanism.* ***Conclusion:*** *There is no evidence to support or reject the hypothesis that hypoxia reperfusion occurs in TMJ OA, and limited evidence is provided to support that hypoxia-reperfusion injury occurs in OA of the knee joint. Since the studies suggest differences between OA and other types of arthritis in relation to hypoxia-reperfusion mechanisms, further research in this field needs to distinguish OA from other types of arthritis.* J OROFAC PAIN 2012;26:233–239

Key words: free radicals, osteoarthritis, reperfusion injury, temporomandibular joint

Osteoarthritis (OA) is the most prevalent chronic disorder in synovial joints. It is considered to be a degenerative process, affecting the synovium, bone, and cartilage, eventually leading to destruction of articular tissues. Furthermore, the disorder has an inflammatory component accounting for many of the clinical signs and symptoms.

The temporomandibular joint (TMJ) is a relatively small synovial joint. In the TMJ, OA is clinically associated with pain, impairment of function, and sometimes with joint sounds such as clicking and crepitation. These symptoms are rather common among the general population. The prevalence of clinically significant TMJ-related pain has been estimated to be at least 5%.[1] The majority of patients with OA of the TMJ are female.

The spin-off for the pathologic process is when the equilibrium between mechanical load and the adaptive capacity of the joint is

disturbed and degradation of the articular tissues dominates regeneration. In this stage, more neuropeptides are formed in the retrodiscal tissue.[2] Cytokines, such as interleukins (IL-1α, IL-1β, IL-6) and tumor necrosis factor–alpha (TNF-α), are formed, but also pain-associated cytokines such as bradykinin. Cytokines induce generation of matrix-degrading enzymes, prostaglandins, arachidonic acid, and isoprostanes. In some of these processes, free radicals are formed.

It is frequently stated that these reactive oxygen species (ROS) play an important role in the etiology of the disease. Free radicals can damage important molecules of the articular tissues and synovial fluid as well as trigger cellular responses that may lead to degenerative joint disease.[3,4] It has been suggested that, in the arthritic joint, there are several mechanisms by which these free radicals are produced. One of the most prominent of these is thought to be hypoxia-reperfusion injury.[2,5–7] This theory was first proposed by Woodruff et al as a possible explanation for the persistence of synovial inflammation.[8] They stated that oxygen-derived free radicals may be produced by recurrent reperfusion injury in joints subjected to repeated pressure changes. Their view was mainly based on the ischemia-reperfusion model proposed by McCord in which the enzyme xanthine oxidase plays an important role in ROS induced dysfunction in ischemic diseases of the heart, bowel, liver, kidney, and brain.[9]

According to the hypoxia-reperfusion mechanism, normal mechanical loading may result in an intra-articular pressure rise that exceeds the end-capillary perfusion pressure, due to an increased pressure within the arthritic joint space, causing hypoxia in the affected articular tissues. Under these hypoxic conditions, cells may rapidly undergo metabolic changes. When loading is released, the intra-articular pressure decreases and perfusion of the affected tissues is reestablished. During reperfusion, free radicals are formed. In the arthritic joint, the equilibrium of the production of free radicals and scavengers of free radicals is disturbed. Due to this imbalance, free radicals can damage the involved tissues and substances such as lipids and immunoglobulin G (IgG). Hyaluronic acid, a key molecule of the lubrication system and of the protection of articular cartilage, is also susceptible to degradation by free radicals, which can eventually lead to inadequate lubrication, vulnerability of the articular cartilage, and increased friction between articular surfaces.[10]

Free radicals are generally unstable and highly reactive because of their capability of independent existence and because they have one or more unpaired electrons in their outer orbits. Free radicals will react with adjacent molecules, stealing an electron to achieve a paired electron configuration. By this reaction, the attacked molecule in turn becomes a free radical because there is now an unpaired electron in its outer orbit. This chain reaction continues, theoretically, until two free radicals react with one another.[2,11,12] The vulnerability of specific molecules to modification by free radicals depends on their structure. Molecules such as fibronectin and hyaluronic acid appear to be extremely vulnerable, while other molecules (eg, type I collagen, albumin, and matrix metalloproteinases) appear to be relatively resistant.[1] Free radicals can also affect the production of molecules involved in the pathogenesis of TMJ OA, eg, IL-1α, IL-1β, and IL-6, by activation of gene transcription.[2]

The hypoxia-reperfusion injury theory is embraced as a plausible model to explain a part of the processes involved in OA in synovial joints, including the TMJ.[2,5–7] However, a model should not only be biologically plausible, but should also be supported by scientific evidence. Therefore, the aim of this study was to determine the available evidence in the literature for whether hypoxia-reperfusion injury plays a role in the pathogenesis of joint diseases in general, and of OA of the TMJ in particular.

Materials and Methods

To retrieve the available evidence for the hypoxia-reperfusion injury mechanism, the search strategy outlined below was followed. Note "tourniquet" was used as a thesaurus term for exclusion because, in articular surgery of the knee, the tourniquet is often used to control intraoperative bleeding and several studies have aimed at determining hypoxia-reperfusion injury induced by the use of a tourniquet instead of determining hypoxia-reperfusion injury as a result of a pathophysiologic process involved in OA.

Inclusion Criteria

All randomized controlled trials (RCTs), controlled trials, systematic reviews, and meta-analyses aiming at providing evidence to support or reject the hypoxia-reperfusion injury mechanism in human synovial joints in relation to osteoarthritis and not induced by the use of a tourniquet were identified and included.

Data Sources

Relevant articles were searched using PubMed/Medline, EMBASE, and Cochrane Central Register

Table 1 Thesaurus Terms and Search Strategy

PubMed	EMBASE	CENTRAL
#1: reperfusion injury	#1: reperfusion injury [tw]	#1: reperfusion injury
#2: #1 AND joints	#2: #1 AND joints	#2: #1 AND joints
#3: #2 NOT tourniquet	#3: #2 NOT tourniquet	#3: #2 NOT tourniquet

of Controlled Trials (CENTRAL). Of all relevant articles, the references were checked for additional useful articles (snowball). Also, a cited reference search was performed with the relevant articles.

Search Strategy

All data sources were searched up to October 2011. In PubMed and CENTRAL, mesh terms as well as free text keywords were used as thesaurus terms. In EMBASE EMTREE terms and text key words were used. An overview of the terms used and the selection process are presented in Table 1 and Fig 1, respectively.

Study Identification

First, the titles, abstracts, and keywords of all identified articles were screened to determine whether they were relevant to the subject of this review. Of the studies examining the hypoxia-reperfusion injury mechanism, all citing articles and all cited references were checked for additional articles. Relevant articles were included for full text reading.

Data Extraction

Studies were included if they had been performed in humans, ie, in vivo or ex vivo, reported comparison of test results with baseline measurements or golden standard, and did not include patients with other joint pathology than arthritis. Two reviewers independently extracted data from the included studies. Contents of the data extraction included size and composition of the studied groups, the part of the hypoxia-reperfusion injury that was studied, baseline and outcome measurements, and applied statistical analysis.

Quality Assessment

Two reviewers independently assessed the quality of each study. Strengths and weaknesses of the study design, implementation, and data analysis of each study were analyzed. Disagreements on quality items were resolved by discussion. Assessment items were *(1)* What was the size and composition of the studied groups?; *(2)* Were inclusion and exclusion criteria for subjects clearly stated?; *(3)* Were the measuring methods clearly described?; and *(4)* Was data analysis clearly described?

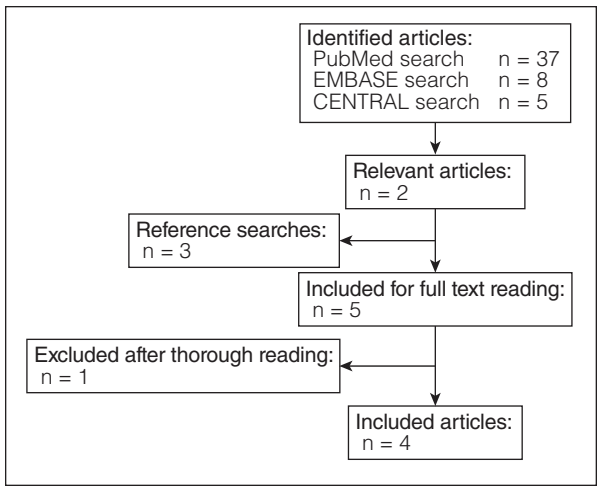

Fig 1 Flowchart of the study selection procedure.

Data Analysis

All analyses were based on the specific numerical data provided in the published articles. Four different parts of the hypoxia-reperfusion injury were investigated in the included studies, reflected in the following outcome variables: intra-articular pressure, lipid and IgG damage, synovial capillary blood flow, and generation of ROS.

Results

A total of 36 articles and one response to an article were identified in PubMed. Eight articles were found in EMBASE. In the Cochrane library, one systematic review, one abstract, two articles, and a response to one of the articles were identified. Of the relevant articles, all citing articles and all cited references were checked, resulting in three additional articles (see Fig 1).

The search strategy resulted in five studies that were selected after reading the title, abstract, and key words. All five were subsequently read in full

Table 2 Description of Included Studies

Author		Study design*	Joint location	Group size	No. and disease	Outcome measures
Blake et al[14§]	(1)	1	Knee	11	11 rheumatoid arthritis	IAP†
	(2)	1	Knee	10	5 rheumatoid arthritis 2 gout 1 Reiter's disease 1 psoriatic arthritis 1 inflammatory arthritis	SCBF‡
	(3a)	2	Knee	Exercise: 19 Control: 15	34 rheumatoid arthritis	Oxidative damage to lipids and IgG
	(3b)	2	Knee/ shoulder	Exercise: 10 Control: 9	10 rheumatoid arthritis 4 ankylosing spondylitis 2 Reiter's disease 2 inflammatory arthritis 1 idiopathic monoarthritis	
Merry et al[15]		1	Knee/ shoulder	Chronic: 8	4 rheumatoid arthritis 2 psoriatic arthritis 2 inflammatory osteoarthritis 1 ankylosing spondylitis	IAP†
				Acute: 5	5 acute traumatic knee effusion	
Jawed et al[16]		1	Knee	5	5 acute traumatic effusion (ATE)	IAP†
				12	7 rheumatoid arthritis (RA) 5 psoriatic arthritis (PsA)	
				7	7 OA	
				9	7 pyrophosphate arthropathy (PA) 1 Behcet's (B) 1 amyloid arthritis (AA)	
Singh et al[17]		1	Knee	4	4 primary OA	Generation of ROS
				2	2 rheumatoid arthritis	

*1: Observational study design, 2: RCT
†Intra-articular pressure
‡Synovial capillary blood flow
§Experiment numbers in parentheses.

text. After thorough reading, one of the studies did not match the inclusion criteria.[13] In this study, only rheumatoid arthritic joints were examined and no osteoarthritic joints. As a result, four studies were included. The major characteristics of the included studies are summarized in Table 2.

The Four Studies

Three of the included studies examined the intra-articular pressure of the knee or shoulder (Blake et al,[14] Merry et al,[15] Jawed et al[16]), one study examined the oxidative damage to lipids (Blake et al[14]), one study examined the synovial capillary blood flow (Blake et al[14]), and one examined the generation of ROS (Singh et al[17]). It seemed reasonable to group the studies that examined the intra-articular pressure, although a meta-analysis could not be performed because of important differences in study design.

One of the included trials used randomization techniques (Blake et al[14]). In this study, the method used to generate the sequence of allocation was not stated. None of the included studies was single or double blinded. Two studies defined patient groups well, stating disease category, distribution of sex, and distribution of age (Blake et al,[14] Merry et al[15]). The other two studies described patient groups identically, but did not mention the distribution of

Main result
Baseline: 10 (SD 6) mmHg Exercise: 170 (SD 74) mmHg
90% (SD 7.77) SCBF reduction during exercise
Significant rise in TBARS after exercise Significant rise in IgG/UVIgG after exercise
Rest: 19.6 (SD 23.5) mmHg Exercise: 222.5 (SD 158.6) mmHg
Rest: ATE: 6 (2-12) mmHg RA: 8 (5-47) mmHg PsA: 18 (11-31) mmHg OA: 17 (7-21) mmHg PA: 25 (9-29) mmHg B: 12 mmHg AA: 14 mmHg Exercise: ATE: 9 (7-16) mmHg RA: 56 (33-150) mmHg PsA: 52 (43-85) mmHg OA: 56 (20-116) mmHg PA: 53 (41-65) mmHg B: 57 mmHg AA: 47 mmHg
Rheumatoid synovium: 28% increase of signal height OA and rheumatoid synovium together: 36% increase of signal height

sex (Jawed et al,[16] Singh et al[17]). None of the studies stated inclusion and exclusion criteria for patient selection. All included studies used small experimental patient groups (varying from eight to 19 patients). Three studies were performed after the approval of an ethical committee was obtained (Merry et al,[15] Jawed et al,[16] Singh et al[17]).

Intra-articular Pressure

Three studies compared intra-articular pressure during rest to that during exercise (Blake et al,[14] Merry et al,[15] Jawed et al[16]). Each of these three studies used isometric quadriceps contractions as an exercise, and time and position of rest before exercise were clearly stated. Nevertheless, a meta-analysis could not be performed on data from the articles studying intra-articular pressure because of important differences in study design. In total, eight patients with OA of the knee and one patient with OA of the shoulder were examined to determine the intra-articular pressure before and during exercise. Intra-articular pressures varied between 6 and 21 mmHg (mean 15.6) before exercise and between 20 and 146.7 mmHg (mean 71.1) during exercise.

Synovial Capillary Blood Flow

Blake et al[14] reported a mean synovial capillary flow rate baseline between 10 and 22 perfusion units in healthy volunteers. During exercise, there was a small drop in capillary blood flow in two of three patients. Reported mean baseline capillary flow rates in inflamed knees ranged between 33 and 372 perfusion units. During exercise, capillary flow fell sharply to means of 4 to 47 units. After exercise, the blood flow returned to baseline or suprabaseline levels within 10 to 15 seconds. In some recordings, reperfusion seemed to be delayed for up to 1 minute after cessation of the exercise. The reported reduction during exercise in the inflamed knees was 90% (SD 7.8), and a mean increase of perfusion after exercise was reported of 1.8% (SD 4.8).

Generation of ROS

Singh et al[17] reported that their results, obtained from electron spin spectroscopy of ex vivo human synovial tissue, indicate that the oxidizing capacity of ROS produced by human synovial tissue varies with the degree of inflammation present. When subjected to hypoxia followed by reoxygenation after 60 minutes, severe inflamed synovium, rheumatoid as well as osteoarthritic, induced an increase in the rate of oxidation of 3,5-dibromo-4-nitroso-benzene sulphonate. This resulted in a 28% increase in signal height at 120 minutes compared to control specimens exposed to continuous hypoxia. In mild inflamed synovium, there was no appreciable difference between specimens subjected to a hypoxia-reoxygenation cycle and control specimens. Application of the xanthine oxidase inhibitors oxypurinol or amflutizole resulted in, respectively, 82% and 26% reduction in the signal height compared to control samples.

Oxidative Damage to Lipids and IgG

Blake et al[14] reported a significant rise in synovial fluid thiobarbituric acid reactive substances (TBARS)

obtained from patients with rheumatoid arthritis of the knee after exercise compared to pre-exercise levels. The greatest rise was measured at 6 minutes after exercise. There was no significant difference in the non-exercise control group between baseline levels and after every 2 minutes until the knee was dry. At 6 minutes, the mean change of TBARS from baseline was 0.44 (SD 0.57) nmol/ml in the exercise group and –0.14 (SD 0.65) nmol/ml in the non-exercise control group.

A similar exercise versus nonexercise protocol was used to determine the level of total IgG present in the synovial fluid. Samples were batch assayed for total IgG and fluorescent IgG (*IgG) by gel permeation high performance liquid chromatography separation and subsequent quantification with ultraviolet (UV) and fluorescence detectors. The fluorescence was expressed as a ratio to the UV absorbance of the IgG peak. In the non-exercise control group, there was no significant rise in *IgG/UVIgG throughout the protocol. In the exercise group, there was a significant rise in *IgG/UVIgG from baseline, greatest immediately after the exercise period, with a mean rise of 0.034 (SD 0.018). Only one of the patients from whom these data were obtained had inflammatory OA.

Discussion

The hypoxia-reperfusion theory is one of the theories proposed to explain some of the pathophysiological processes involved in OA of the TMJ.[2,5–7] An intensive literature search did not uncover studies that investigated the hypothesis that the hypoxia-reperfusion mechanism is involved in TMJ OA. However, four studies were retrieved that investigated whether this mechanism could be involved in OA in other joints, eg, the knee and shoulder. Thus, no direct evidence for the existence of the hypoxia-reperfusion injury mechanism in TMJ OA was found. Positive but weak evidence seems to support the hypothesis that this mechanism is involved in OA of the knee, which could be at most indirect evidence for its involvement in TMJ OA. Possibly the unfamiliarity with the TMJ of most researchers who investigate pathophysiologic mechanisms of OA and the problematic accessibility of the TMJ may account for the fact that this hypothesis was never experimentally tested for TMJ OA.

The mechanism of hypoxia-reperfusion injury is mainly based on the following hypotheses. Firstly the intra-articular pressure must exceed the end-capillary perfusion pressure, so that the perfusion of the affected tissues decreases to an extent that allows hypoxia to occur. Secondly, ROS must be generated after reoxygenation of the hypoxic tissue. Thirdly, when the affected tissues are reperfused, the ROS cause damage to substances such as lipids and IgG. Presumably, synovial fluid oxygen tension should drop during the hypoxia stage and rise again during the reperfusion stage. The selected studies investigated one or more of these hypotheses. The outcomes of these studies seem to provide some support for the hypoxia-reperfusion theory.

Although there are many similarities, the TMJ differs in some aspects from other load-bearing synovial joints. The articular surfaces are covered by fibrocartilage rather than hyaline cartilage. And, at the molecular level, the TMJ has a characteristic distribution of extracellular matrix molecules.[9,18–21] Although fibrocartilage and hyaline cartilage both consist of collagen, large and small proteoglycans, and water, the major collagen species of fibrocartilage is type I collagen. This is unlike the hyaline cartilage of other joints, in which type II collagen is the major collagen species.[20,22] These specific features of the TMJ make it difficult to extrapolate data obtained from other joints to the TMJ. Knowledge of specific mechanisms and the tissues involved is indispensable for making assumptions allowing extrapolating research outcomes from one joint to another. Nevertheless, findings from other joints may provide a meaningful basis for formulating research hypotheses for the TMJ.

In the studies described above, different types of arthritis have been investigated. Blake et al[14] grouped the different arthritides together and did not describe their findings according to the different arthritis types. Merry et al[15] and Singh et al[17] reported arthritis type-specific as well as arthritis type nonspecific findings. Only Jawed et al[16] specifically distinguished the findings obtained from OA joints from those of joints having other arthritides. This distinction is important because possible differences between arthritides can give rise to new directions in research.

Apart from the hypoxia-reperfusion injury, other mechanisms may produce ROS that may act simultaneously or independently from the hypoxia-reperfusion mechanism.[2,11,23] When molecules are subjected to extreme shear stress, ROS can be formed by homolytic fission.[2,11,24] Furthermore, when microbleeding occurs within the vascularized tissues of a joint, hemoglobin could produce a fenton reaction and catalyze the production of damaging hydroxyl radicals.[25] Hemoglobin also could contribute to the formation of highly reactive ferryl radicals. Other proposed mechanisms are ROS production during arachidonic acid catabolism, ROS generated in response to cytokines, and ROS

production by the peroxynitrite pathway.[11,24] It is not clear which of these mechanisms do occur in osteoarthritic joints and, if so, to which extent they contribution to the disease.[23] It is, however, possible that ROS play an important role in the disease process, even when hypoxia-reperfusion injury would not occur.

For improvement and development of new treatment modalities for TMJ OA, it is essential to understand the underlying pathologic mechanisms. Therefore, future research may focus on clarifying the origin of ROS in OA and investigating to which extent research outcomes from large synovial joints can be extrapolated to the TMJ.

Conclusions

All included studies used small experimental patient groups. Furthermore, no studies were found that used homogeneous OA groups. Instead, the majority of these groups contained a variety of arthritides and not exclusively OA. The heterogeneity and the small size of the patient groups do not permit firm conclusions. The studies also do not provide any evidence to support or reject the hypothesis that hypoxia-reperfusion plays a role in TMJ OA. Positive but weak evidence supports the hypothesis that hypoxia-reperfusion injury occurs in OA in the knee.

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