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Review

Osteoarthritis of the temporomandibular joint: a review of aetiology and pathogenesis

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Abstract

The aim of this review was to assess the level of evidence for genetic, biological, and functional predictive and predisposing factors for end-stage temporomandibular joint arthritis within the published literature. A comprehensive review based upon PRISMA guidelines was performed from all literature relevant to the topic. Case series and animal studies were included given the rare nature of the disease and goal of finding root-cause predictive factors. Clinical and radiographic measures were used specifically to identify factors which may have contributed to disease onset and progression. A total of 249 abstracts were identified based on search terms of major databases. After application of exclusion and inclusion criteria, 63 full-text articles were included in the analysis of this paper. There were few factors that could be reliably used to predict end-stage temporomandibular joint disease. Limited evidence is available to adequately predict end-stage temporomandibular joint osteoarthritis. No descriptive process exists that explains how and why this process can occur in younger adults. A better understanding of the aetiology and pathogenesis of TMJ-OA may lead to prevention and more effective management strategies that may reduce the need for drastic surgical intervention, particularly in young adults.

Keywords: Temporomandibular; Joint; Osteoarthritis; Young; End-stage

Introduction

Temporomandibular joint osteoarthritis (TMJ-OA) continues to be a diagnostic and treatment challenge. Temporomandibular joint (TMJ) arthropathy exists within a spectrum of facial pain syndromes, and its presentation can vary significantly from osteoarthritis of the other joints of the body. TMJ-OA is a degenerative disease of the joint, which culminates in the progressive destruction of all soft and hard tissue components of the TMJ. Whilst once regarded as a disease of the elderly, it appears that this is incorrect; rather, a culmination of risk factors over time contribute to the development of this disease.[1]

Current diagnosis of TMJ-OA is based on complex clinical and radiographic criteria. Clinical criteria alone have low sensitivity and specificity for the diagnosis of this condition.[2,3] Typically, radiographic investigation of TMJ pathology involves both CT for bony imaging, and MRI for imaging of the disc and soft tissue relationships. However, such radiographic findings may not always correlate with the clinical presentation of TMJ symptoms.[4,5] In patients who present in early adulthood with severe clinical symptoms and catastrophic radiographic changes, there are significant implications for management, including the potential need for early total joint replacement.[6] In these patients, it is not uncommon that multiple risk factors exist that contribute to late-stage disease, with no clear single causative factor.[7]

Most clinical research into osteoarthritis has focused on more common presentations of this disease in the hip and knee. General risk factors for osteoarthritis in these joints have been well-described in the literature.[8] Less evidence is available on the specific risk factors relevant to TMJ osteoarthritis, as well as the underlying pathophysiology that results in clinical disease, though it seems inflammation may play a significant role.[9]

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It is evident that there is a need to identify factors that may be implicit in the development of end-stage TMJ disease before joint replacement is indicated. The aim of this literature review was to identify aetiological features that may serve as clinical predictors for TMJ-OA, with a particular focus on factors which may contribute to early TMJ osteoarthritis in otherwise healthy individuals.

Aims and methods

Aims

The aims of this review were twofold. First, to identify genetic, functional, and biological predictive and predisposing factors in the aetiology of temporomandibular osteoarthritis; and secondly, to identify which of these factors may be implicated in the early development of osteoarthritis.

Search strategy

An electronic literature search was performed on September 2, 2018. A total of 249 abstracts were gathered from major information sources including PubMed, Google Scholar, and ScienceDirect. Additional manual searches were performed of reference lists from the included studies (Fig. 1).

Search queries involved keyword searches, used both alone and in combination, based on syntax rules relevant to the search engine: (temporomandibular* or TM* or TMJ*), (arthritis), (joint* or joints*), (end-stage* or severe* or catastrophic* or advanced*), (degeneration* or disease*), (aetiology* or causative* or predisposing* or predictive* or risk factor*), (biologic* or biological* or biomechanical*), (gene* or genetic* or inherited*), (anatomic* or anatomy*), (radiographic* or MRI* or CT*), (occlusion* or dental* or occlusal*), (facial morphology* or facial type* or brachyfacial* or mesofacial* or dolichofacial*), asymmetry, (parafunction* or bruxism* or clenching* or grinding*), (derangement* or internal derangement* or anterior disc displacement*), (trauma* or fracture* or mandible fracture* or condylar fracture*), (hypermobility* or laxity*).

Inclusion/exclusion criteria

Studies were selected for inclusion if they reflected the primary research question of the literature review. Study designs included systematic reviews, randomised controlled trials, cohort studies, and case-control studies. As this literature review is to assess for predictive or predisposing aetiologic factors in temporomandibular osteoarthritis, isolated case series regarding early onset temporomandibular osteoarthritis were included. Due to the limited availability of human aetiological studies, animal studies were included. English language-only articles were included in the study.

The exclusion criteria included:

1. Research not relevant to the aims of this review
2. Studies lacking sufficient outcome measures (clinical and radiographic)
3. Research from journals that did not have a documented, transparent peer-review process, and published conference abstracts.

Study selection

All authors (GD and SD) reviewed the studies to determine their relevance to the literature review, based upon the abstracts. SD then read the full-text versions of the eligible articles and were referenced in the literature review as required. There were no disagreements between authors regarding the utility or relevance of any article to the writing of this manuscript.

Risk of bias was minimised by using established Cochrane guidelines. Methodological quality of studies was evaluated based upon the World Health Organization (WHO) Levels of Evidence as reproduced in Table 1.

Results

A total of 249 abstracts were identified based on search terms of major databases. After application of exclusion and inclusion criteria, 42 full-text articles were included in this review. Despite a large number of articles included in the study, some major flaws were evident with regards to the homogeneity of study design, as well as outcome measures of each. Among the 42 papers, only a select number directly outlined a definition of ‘osteoarthrosis’ or ‘osteoarthritis’ and this was often based on a group of clinical or radiographic characteristics that were not consistent amongst studies. Furthermore, all animal studies were based on histological features of early osteoarthritis only, whereas clinical studies were largely focused on clinical and radiographic features.

Subgrouping of articles

Given the broad variation and lack of homogeneity in study designs and research methodology, full-text articles that met criteria for inclusion were divided into three categories: anatomical risk factors, biomechanical risk factors, and biological/genetic risk factors. This categorisation was necessary for several reasons. First, within each category, study designs were generally similar and allowed for better comparative analysis. Secondly, papers examining for biological/genetic risk factors for TMJ arthritis were heavily based upon animal and *in vitro* studies. Thirdly, biomechanical and anatomical risk factors were based upon a mix of animal and clinical studies and required separate consideration.

Individual studies are listed in Table 2, with the listing based upon main topic of study, and analysed based upon study design, level of evidence, and main findings.

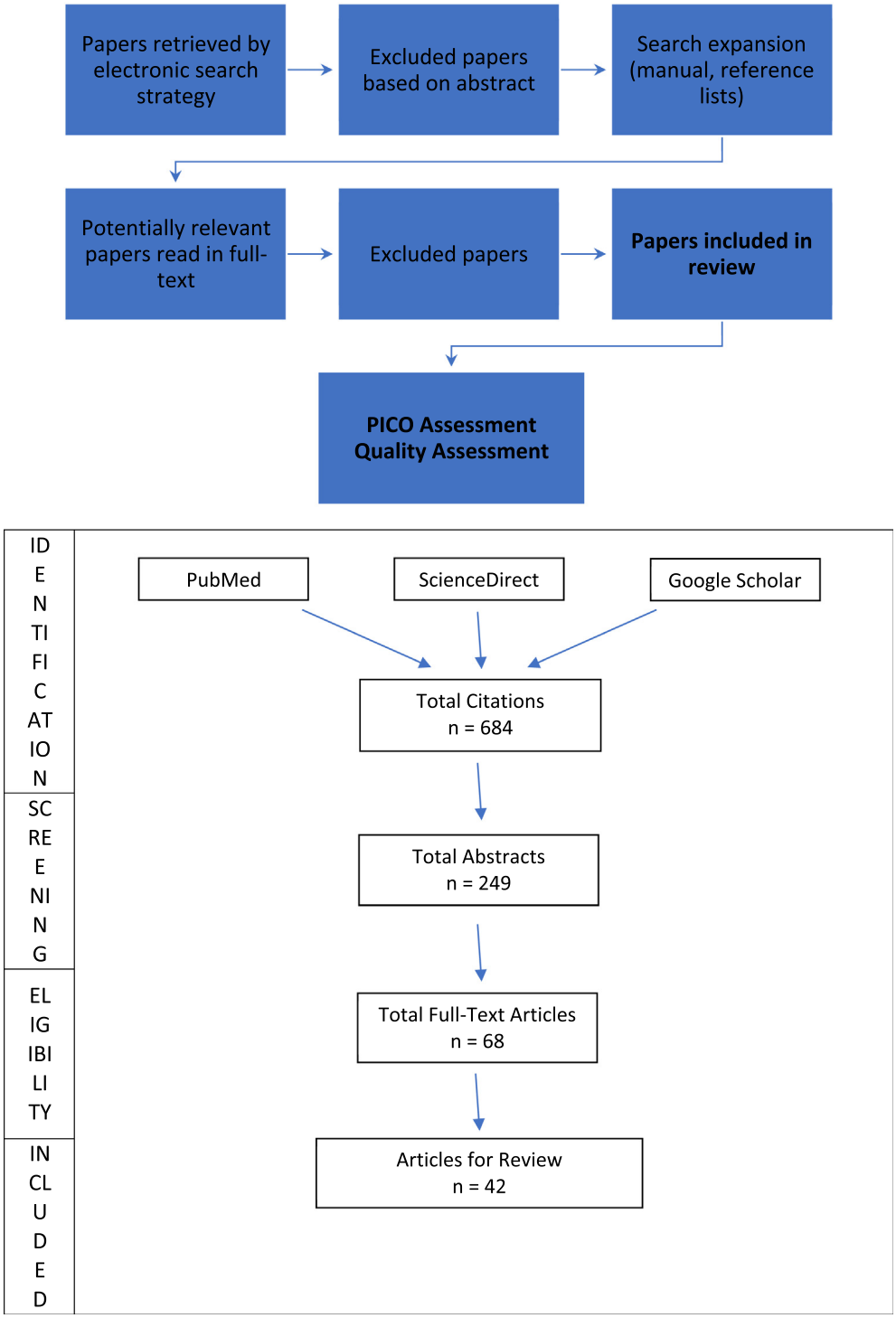

Fig. 1. Literature review methodology and search strategy.

Anatomical risk factors

Dental malocclusion

The hypothesis that malocclusion was strongly associated with temporomandibular disorder has largely been disproven.[11–13] Obrez and Turp have previously suggested a reverse causation effect, whereby the presence of painful TMDs can influence mandibular position and movements, possibly leading to occlusal disturbances.[14] Certain occlusal factors including anterior open bite, bilateral open bite, negative overjet, large overjet, unilateral scissor bite in men, and edge-to-edge bite in women, have been found to be weakly associated with TMD.[12,15] Bell et al, in a prospective study,

Table 1
World Health Organization Levels of evidence.

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

used a randomised, double-blind model of artificial occlusal interferences, and found that whilst introduction of occlusal interferences could worsen existing TMD symptoms, they did not result in TMD in previously well patients.[16] Manfredini et al in their recent systematic literature review also concluded that there is no disease-specific association between dental occlusion and TMD.[13]

One major caveat of most publications in this category was the lack of radiographic outcome measures; clinical symptoms of TMD were assessed, but there was no correlation with joint degeneration. Hence, whilst some weak conclusions can be made regarding dental occlusion and TMD, there is only circumstantial evidence of a direct correlation with TMJ OA. One exception is that of Pullinger and Seligman, who through an observational study of 381 female patients determined that those with osteoarthrosis were most consistently characterised by a difference in centric occlusion and centric relation of greater than 2mm, a large overjet (>5mm), and reduced overbite, but this was only significant in extreme ranges of occlusal measurements.[17]

Facial morphology

The relationship between degenerative disorders of the TMJ and facial morphology has been examined in detail by Manfredini et al.[18] Across the 34 articles described in their review, eight assessed for MRI findings of TMJ-OA, and separately, clinical signs and symptoms of disc displacement and other temporomandibular disorders. Whilst the quality of literature was moderate, low in volume and heterogeneous in methodology, the conclusion was that skeletal class II profiles, short ramus height, and hyperdivergent growth patterns may correspond with a greater risk of TMJ dysfunction and osteoarthritis.

Biomechanical risk factors

Friction and adhesive forces

Frictional forces have long been thought to play a definitive role in progression of osteoarthritis, however this is largely expert opinion[19,20] without strong experimental evidence. The current prevailing theory is that joint overload occurs, past a joint's adaptive capacity.[2,21–23] In a human model of patients with pre-existing features of joint overload, in the form of bruxism, Kopp et al performed synovial aspirates and noted changes in the physicochemical properties of synovial fluid of the TMJ.[24] This loss of lubrication may theoretically contribute to joint wear and degeneration, at least through basic biomechanical principles.[25–26] More recently, inflammation and the specific roles of reactionary enzymes in this process have been identified in genetic mouse models (HtrA1 Ddr2 and MMP-13), which can cause further injury, compounded by a limited blood supply and ability to clear toxins.[27]

Parafunction

There is a large discrepancy in the literature as to the relationship between parafunction and TMJ degeneration. Animal studies have identified histological features of osteoarthritis in models of excessive loading and parafunction of the TMJ.[28,29] This finding was paralleled in a human observational study by Israel et al.[30] In this large study of 124 joints, patients with existing, severe symptomatic TMJ disease underwent radiographic investigation and subsequent arthroscopy, for both diagnostic and therapeutic purposes. Where patients with a history of excessive loading, or laterotrusive/protrusive parafunctions, there was a statistically significant relationship between parafunction and arthroscopically-diagnosed osteoarthritis.

This conclusion was disputed by Pullinger and Seligman examining for the relationship between bruxism-related tooth wear and types of temporomandibular disorders in symptomatic and asymptomatic patients, and found no association between attrition score and temporomandibular osteoarthritis.[31] Due to an ongoing lack of consensus in the literature, the same authors later published another similar study on the relationship between occlusal variables and joint osteoarthritis, and reached the same conclusion.[17] John et al, in a study of 208 TMD patients and 172 control patients, also found no association between dental signs of bruxism and clinically-diagnosed TMD; while his population group included those with clinical features of osteoarthritis, this was not differentiated from the other diagnoses within the TMD group.[32]

Clenching, as a separate parafunction to grinding, may theoretically increase biomechanical load on the TMJ leading to degeneration; this has been demonstrated in a three-dimensional finite element models of the mandible.[33,34] However, there is no clinical evidence to support this conclusion.

Table 2
Summary of literature examined, subgrouped into anatomical, biomechanical, and biological/genetic risk factors.

Main topic of study	First author, year and reference	Study design	Level of evidence	Main findings
Anatomical risk factors:				
Dental malocclusion and signs of TMD	Gesch, 2004[11]	Population based survey study	III	4310 men and women aged 20-81 A weak association between TMD signs/symptoms and malocclusion/functional occlusal factors. A bilateral open bite up to 3mm was clinically relevant and associated with TMD signs (OR 4), but this pattern is very rare. No investigation of osteoarthritis
Dental malocclusion and Symptoms of TMD	Gesch, 2005[12]	Population-based survey study	III	No occlusal factors examined correlated with frequent subjective tmds Frequent clenching was connected with subjective TMD symptoms (OR 3.4) No investigation of osteoarthritis
Occlusal interference and masseter activity	Michelotti, 2005[70]	Double-blind randomised crossover experiment – human subjects	IIb	Active occlusal interference caused a significant reduction in the number of activity periods per hour and in mean amplitude. No signs of TMD No investigation of osteoarthritis
Dental malocclusion and TMD	Gesch, 2004[11]	Population-based survey study	III	Malocclusion weakly associated with TMD included unilateral open bite, negative overjet, unilateral scissor bite in men, and edge-to-edge bite in women. No investigation of osteoarthritis
Association between TMD and malocclusion	Obrez, 1998[14]	Systematic literature review	III	The presence of painful tmds may influence mandibular position and movements, possibly leading to occlusal disturbances No investigation of osteoarthritis
Effect of occlusal interference on TMD	Bell, 2002,[16]	Randomised double-blind experiment – human	IIb	Occlusal interference does not cause TMD symptoms in previously well patients, but can worsen TMD symptoms in patients with prior TMD. No investigation of osteoarthritis
Relationship between skeletal pattern and malocclusion	Alm şan, 2013[71]	Prospective, observational, analytic study	III	The following occlusal factors showed a possible correlation with TMD: Midline shift Large overjet Deep overbite No investigation of osteoarthritis
Relationship between malocclusion and TMD	Thilander, 2002[15]	Observational study	III	TMD is significantly associated with posterior crossbite, anterior open bite, Class III malocclusion, extreme maxillary overjet No investigation of osteoarthritis
Relationship between occlusal factors and TMD	Pullinger, 2000[17]	Observational study	III	Patients with disc displacement mainly characterised by unilateral posterior crossbite and longer CO/CR slides Patients with osteoarthrosis most consistently characterised by longer RCP-ICP slides and larger overjet, and reduced overbite. Significant relative risk for disease (Odds ratio >2) associated with extreme rranges of occlusal measurements.
Occlusal adjustment to improve TMD	Koh, 2004[72]	Systematic literature review	III	Insufficient data for treatment or prophylaxis of TMD by occlusal rebalancing No assessment of osteoarthritis
Bruxism and osteoarthritis	John, 2002[32]	Observational study	III	No association between bruxism, assessed by incisal tooth wear, and clinically-diagnosed osteoarthritis
CO-CR slide and TMD	Weffort, 2010[73]	Case-control study	III	Large CR-CO slides associated with TMD symptoms No assessment of osteoarthritis

(*continued on next page*)

Table 2 (*continued*)

Main topic of study	First author, year and reference	Study design	Level of evidence	Main findings
Facial morphology	Manfredini, 2016[18]	Systematic literature review	III	Skeletal class ii profiles and hyperdivergent growth pattern are likely associated with increased frequency of TMJ disc Displacement and degenerative disorders
Biomechanical risk factors				
Osteoarthritis and internal derangement	de Bont, 1986[22]	Light microscopic study	III	Internal derangement of the TMJ disc is associated with osteoarthritis
Loss of lubricaton	Nitzan, 2001[20]	Expert opinion	IV	Increased friction of the TMJ components is likely a major causative factor in displacement of the articular disc
Loss of lubrication	Nitzan, 2003[19]	Expert opinion	IV	Increased friction of the TMJ components is likely a major causative factor in displacement of the articular disc
Dietary loading and TMJ degradation	Liu, 2014[28]	Animal (mouse) study – control group Histological analysis	III	Thinner and degraded cartilage, reduced cartilage cellular density, decreased expression of collagen II and aggrecan, loss of subchondral bone and enhanced osteoclastic activity were observed in tmjs of both groups, but worst in excessive dietary loading. Dietary loading exacerbates TMJ osteoarthrosis
Relationship between parafunction and arthroscopically-diagnosed osteoarthritis	Israel 1999[30]	Case-control study	III	Parafunctional masticatory activity and its influence on joint loading contribute to osteoarthritis of the temporomandibular joint
Laterotrusive and protrusive movements and mechanical stress on the TMJ	Gallo, 2006[74]	Human fmri study	III	Parafunction may produce compression and shear forces capable of initiating disc displacement and condylar and articular eminence degenerative changes
Effect of lateral pterygoid function/parafunction on mandibular condyle position	Hiraba, 2000[75]	Human EMG study	III	Parafunction of the lateral pterygoid can lead to TMJ internal derangement and osteoarthrosis
Attrition and TMDS	Pullinger, 1993[31]	Case-control study	III	Dental attrition does not correlate with existence or severity of temporomandibular osteoarthrosis
Occlusal disturbance and TMDS	Seligma, 1991[76]	Case-control study	III	Large, asymmetric RCP-ICP slides are the only occlusal interference associated with temporomandibular joint osteoarthrosis
Repeated mouth opening	Fujisawa, 2003[29]	Rabbit TMJ study	III	Repetitive, forced jaw opening parafunction can induce osteoarthritic changes and cartilage degeneration in TMJ osteoarthritis
Macrotrauma	Fisher, 2006[77]	Cohort study	III	Patients with arthralgia or arthritis were 2.0 times more likely to have had a prior head injury
Macrotrauma	Klobas, 2004[41]	Cohort study	III	Patients with a history of whiplash injury are significantly more likely to have tmds but not temporomandibular joint arthroses
Macrotrauma	de Boever, 1996[43]	Cohort study	III	External trauma to the joint or jaw is an important aetiologic factor in the aetiology of TMD, but the prognosis is favourable (no association with long term osteoarthritic symptoms)
Macrotrauma	Probert, 1994[42]	Retrospective	III	Temporomandibular pain and dysfunction infrequently associated with trauma to the temporomandibular joint
Disc displacement	Westesson, 1984[49]	Cadaveric dissection	Iii	Partially or completely anterior disc displacement associated with disc deformation and osteoarthrosis
Joint hypermobility	Kavuncu, 2006[53]	Observational study	III	Systemic and localised hypermobility may have a role in the aetiology of TMD

Joint hypermobility	Conti, 2000[52]	Case-control study	III	No association was found between intra-articular disorders and systemic hypermobility, Internal derangement of the articular disc more likely in patients with TMJ hypermobility
Joint hypermobility and temporomandibular disorder	de Coster, 2005[54]	Observational study	III	All Ehlers-Danlos patients were symptomatic for hypertranslation but no signs osteoarthrosis on OPG
Biological/genetic risk factors:				
Oestrogen-receptor polymorphism	Kim, 2010[55]	Observational study	III	In patients with diagnosed TMD, there was a correlation between oestrogen receptor polymorphism and symptoms but this was not significant
Tgf-b1	Long, 2016[27]	Comparative animal study (genetically modified)	Iii	Elevated tgf-b1 is mechanistically involved in the pathogenesis of tmj oa
Tgf-b1	Xu, 2016[56]	Comparative animal study (genetically modified)	Iii	Tgf-b1 is involved in the degradative pathway of tmj osteoarthritis
Tgf-b1	Wong, 2014[78]	Comparative animal study (genetically modified)	Iii	Tgf-b1 is upregulated in the tmj articular cartilage in chondrodysplasia and can be used as an early diagnostic tool of tmj oa
Vitamin D	Shen, 2013[64]	Animal study (genetically modified)	III	Vitamin D deficiency causes an erosive TMJ OA phenotype by inducing DNA damage, cellular senescence and the production of senescence-associated inflammatory cytokines
Bigylcan/fibromodulin	Wadhwa, 2005[58]	Animal study (comparative genetically modified)	III	Mice deficient in BGN/FMOD causes an imbalance in apoptosis of chondrocytes in articular cartilage, causing abnormal production of structural ECM proteins and premature erosion and degradation of the articular surface
Biglycan/fibromodulin	Embree, 2010[57]	In vitro cellular study	Iib	Overactive TGF-B1 signal transduction due to deficiencies in BGF/FMOD, signal induced chondrogenesis and ECM turnover
Hereditary factors	Michalowicz, 2000[79]	Twin study	Iii	No heritability of tmj signs and symptoms (no mention of osteoarthritis)
Prg4	Hill, 2014[68]	Animal study (genetically modified	Iii	Mice lacking in lubricin have a normal tmj at birth, but develop degeneration resembling tmj osteoarthritis (synovial hyperplasia, deterioration of cartilage/ disc/fossa
Mmp-1	Luo, 2015[69]	Human cohort study	Iii	The susceptibility of 1g2g genotype carriers to addwor with or without tmj oa was also Considerably higher than that of other genotype carriers
Vitamin D polymorphism	Yilmaz, 2018[65]	Observational study	III	Vitamin D receptor polymorphisms may play a role in susceptibility to temporomandibular joint internal derangement and osteoarthritis.

Macrotrauma

Facial trauma has been postulated as a contributing factor to TMJ-OA, via similar physiological pathways as in microtrauma.[35] Direct trauma to any joint may have a range of physiological effects, from mild inflammation to destruction of the hard and soft tissue components.[36]

The incidence of longstanding TMD symptoms following mandibular trauma appears to be low.[37] Tabrizi et al, in a retrospective cohort study of 99 patients, attempted to correlate mandible fracture patterns with post-traumatic signs of temporomandibular disorder (clicking, pain, reduced mouth opening).[38] Whilst not statistically significant, patients with a condylar fracture and contralateral mandibular fracture were more likely to have TMD signs that those with unilateral fracture only. Goss and Bosanquet performed a study of similar design, finding that in patients with post-traumatic TMD symptoms, longstanding cartilage degeneration was evident in 38 out of 40 patients.[39]

Wu et al followed up seven patients with conservatively managed condyle fractures who suffered severe TMJ problems (including ankylosis) subsequent to their trauma, necessitating arthroplasty or joint replacement.[40] In all patients, there was either severe comminution of the condyle, or severe fracture with dislocation. Histological samples obtained during TMJ surgery revealed destruction of condylar cartilage, with severe degeneration of condylar bone.

Macrotrauma to the head and neck region without direct condylar fracture has an unclear relationship with the development of TMJ-OA after injury. Fischer et al showed that adolescents with major head and neck injuries were significantly associated with clinically diagnosed TMJ-OA, but this result was not consistent with other similar studies.[41–43]

It appears that severe condylar trauma with intracapsular involvement of fractures may predispose to osteoarthrosis, but there is no association with generalised macrotrauma to the joint region.

Disc displacement

The natural history of TMJ-OA has typically been thought to start with anterior disc displacement with reduction, gradually becoming anterior disc displacement without reduction, and culminating in degenerative joint disease and osteoarthritis.[44] In a goat animal model, surgically-induced disc displacement resulted in disordered cartilage composition, reduced angiogenesis, and proteoglycan degeneration, all consistent with features of TMJ-OA.[45]

This has been disputed in the literature, as anterior disc displacement does not always lead to TMD due to the adaptive capacity of the cartilage and joint,[46] that disc displacement can spontaneously resolve in a significant proportion of patients,[47] and that in up to 22% of patients with anterior disc displacement with or without reduction, there are no associated degenerative changes on MRI.[48]

Nevertheless, a relationship seems to exist between partial or complete anterior disc displacement and osteoarthritis.[22,49] Osteoarthritis can occur in the absence of disc displacement, but appears to be more severe in patients with associated disc displacement.[48,50] Roh et al further divided anterior disc displacement into cases with and without reduction, and found that joints with anterior disc displacement with reduction had an odds ratio of 2.01 with degenerative changes, whereas joints with anterior disc displacement without reduction had an odds ratio of 4.61.[48] Whilst a direct causal relationship is not well-established in the literature, it appears that internal derangement of the TMJ can significantly increase the risk of osteoarthritis.[47,48,50,51]

Joint hypermobility

Joint hypermobility has been assessed with regard to its relationship to TMD through observational studies only. In otherwise healthy patients with localised joint hypermobility, internal derangement of the articular disc was found to be more likely.[52,53] However, in a study of Ehlers-Danlos syndrome, all patients were symptomatic for joint hypertranslation, but none examined had radiographic signs of TMJ-OA.[54] It does not appear that localised hypermobility has a role in the aetiology of TMJ-OA.

Biological/genetic risk factors

Oestrogen-receptor polymorphism

Given the preponderance of temporomandibular osteoarthritis in women compared with men, the role of gonadocorticoids has been investigated as a potential aetiological factor in the development of this condition. Kim et al performed a cohort study to assess for a correlation between TMD and polymorphism of oestrogen receptors, but no significant relationship was found.[55]

Transforming growth factor β1 (TGF- β1)

TGF- β1 is a secretory cytokine involved in cell growth, proliferation, and apoptosis. Elevated levels of TGF- β1 appears to be mechanistically involved in the pathogenesis of TMJ-OA[27] primarily through promoting the degradation of fibrocartilage.[56]

Animal models have investigated the role of TGF- β1 on the biglycan-fibromodulin pathway of cartilage remodelling. There is strong evidence that TGF- β1 causes a deficiency in biglycan/fibromodulin, leading to an imbalance in apoptosis of chondrocytes, abnormal production of structural ECM proteins and premature erosion/degradation of joint surfaces.[57–58]

1,25-dihydroxycholecalciferol (Vitamin D) deficiency

Vitamin D is a fat-soluble nutrient well-known to have physiologic roles in bone metabolism, serum calcium homeostasis, and cell proliferation and differentiation, primarily through the ubiquitous vitamin D receptor.[59] The majority

of vitamin D is produced endogenously, via a photochemical reaction which converts 7-dehydrocholesterol in the skin to cholecalciferol using UV light; the remainder is obtained from dietary sources.

Vitamin D deficiency has been previously shown to be associated with a number of systemic and age-related diseases, including cardiovascular disease,[60] diabetes,[61] and osteoarthritis of the hip and knee.[62,63] Early animal evidence in genetically-modified mouse models suggests that an absolute deficiency of 1,25-dihydroxycholecalciferol can initiate features of condylar cartilage erosion of the TMJ, through secretion of senescence-associated inflammatory cytokines by senescent chondrocytes.[64–65]

PRG4/lubricin

Lubricin is a major glycoprotein component of synovial fluid, and its encoding gene proteoglycan 4 (PRG4) has been found to be involved in maintenance of cartilage surfaces and regulating proliferation of intimal cells.[66] In human populations, this has been studied primarily in the population group with camptodactyly-arthropathy-coxa vara-pericarditis syndrome, and autosomal recessive condition caused by mutations in the PRG4 gene. Patients with this syndrome are born with normal joints, that rapidly undergo systemic cartilage degeneration, synoviocyte hyperplasia, and osteoarthritis.[67] In a genetically-modified mouse model using animals lacking the PRG4 gene, Hill et al observed that the absence of PRG4, and subsequently lubricin, resulted in the rapid development of severe TMJ-OA.[68]

Matrix metalloproteinase-1 (MMP-1)

The role of MMP-1, an enzyme involved in breakdown of the extracellular matrix, has been examined with relation to the risk of OA developing in at-risk groups. It appears that in patients with certain types of MMP-1 polymorphism, there is a greater conversion rate from anterior disc displacement to TMJ OA.[69]

Discussion

The TMJ is a unique structure. A ginglymoarthrodial joint, the TMJ consists of a fibrocartilaginous articular disc wedged between the glenoid fossa of the temporal bone superiorly, and the mandibular condyle inferiorly. The highly vascularised and innervated retrodiscal tissues lie in close proximity to the functional joint and are attached posteriorly to the disc, while the lateral pterygoid muscle is attached anteriorly. The highly complex anatomical components of the joint (bone, articular disc, other fibrocartilage, synovium, ligaments, muscles, nerves, and vessels) are reflected similarly in the complexity of functions of the joint, which include speech, swallowing, mastication, and facial emotive expression). Understandably, a number of vastly different theories have been put forward to explain the nature of pain and symptoms of TMJ dysfunction.

Osteoarthritis is a degenerative joint disease that is characterised by progressive degradation and thinning of articular cartilage, synovitis, and subchondral bone remodelling.[80] Given the innate complexity and unique features compared to other joints of the body, the assessment and diagnosis of TMJ-OA is difficult. It is clear in the literature that there is often confusion between a formal diagnosis of OA and differentiation from other temporomandibular disorders.

Despite this, the management of early osteoarthritis is similar to this disease in other joints. Rest, physiotherapy, splints, awareness therapy, and dietary advice are available but provide symptom relief only and do not address the underlying disease process. Surgery is indicated where there is a functional limitation associated with joint disease, but limited success rates and significant risk factors imply a strong case is required before operative treatment is indicated.

The ability to detect early TMJ-OA through risk factors is important to prevent situations where there is no other alternative but surgery to manage the patient's symptoms, given the significant risks associated with TMJ surgery and limited access to care.

End stage TMJ disease is usually a presentation to the dentist or GP, which is then referred to oral and maxillofacial surgeons. There may not always be involvement of a rheumatologist until the disease beings to involve other joints.

This review highlights emerging factors that may be important to consider in patients who present with early, destructive temporomandibular osteoarthritis where no clear other aetiology can be identified. Vitamin D shows emergence as a potential aetiological factor that can contribute to early osteoarthritis of the TMJ, but only animal models exist to support this. TGF-B has been implicated in animal models as a potential biomarker for TMJ-OA, as it is shown to be upregulated in situations of severe cartilage degeneration. MMP-1 polymorphism may be the factor that explains why certain patients with anterior disc displacement continue to degenerative joint disease, whereas others spontaneously resolve.

Despite these newer factors, evaluating the risk of early TMJ-OA still involves the documentation of anatomical and biomechanical risk factors, including trauma 80. Whilst there is still little evidence to prove that anatomical factors can contribute to early degenerative joint disease of the TMJ, anatomic variations of the hip and knee (such as meniscal lesions, coxa valga) have been proven to increase risk of osteoarthritis of these joints.[81] It would not be unreasonable to suggest that similar aetiological factors exist for the TMJ, but this relationship has not been identified as yet. With the increasing use of MRI and cone-beam CT, radiographic studies may in future be sufficiently powered to investigate such hypotheses.

Comment must be made on the use of animal models in the investigation of TMJ-OA. TMJ arthritis is a disease of

a very unique and anatomically complex joint, on a complex disease spectrum, with no clear diagnostic guidelines. There has been great difficulty in the attempt to standardise the literature and produce strong aetiological evidence for this condition. Animal models can provide good insight as to the biological nature of the disease process, but with this study design comes a certain lack of universal applicability and clinical benefit. Whilst some animal models can replicate its form and function,[82] the human TMJ is specifically adapted for functions that are nuanced and unique to the species only. More human studies are required to advance this area of research.

End-stage TMJ-OA is therefore a challenging condition. The diagnosis and management strategies outlined in the literature is controversial, and another layer of complexity is added in younger populations where joint replacement may be clinically or radiographically indicated based upon current surgical classifications of TMD. Surgical classifications of TMJ disease suggest that patients in this subgroup will not necessarily benefit from more conservative measures, and the decision to replace a joint in patients under the age of 30 must be carefully considered. Failure to acknowledge mistakes of the past can result in devastating outcomes for patients with this condition.

There are several limitations of this paper which must be acknowledged. TMJ-OA exists on a diagnostic spectrum that is currently without standardisation; radiographic and clinical findings do not correlate with one another, and there is significant overlap between the range of diseases that encompass the broader definition of temporomandibular disorder. Following on from this, there is a paucity of evidence regarding the aetiology of TMJ-OA, and a lack of qualitative homogeneity of the included studies. Even within the subgroup of individuals with radiographically-proven, end-stage destructive changes of osteoarthritis, there may be no associated symptoms indicating a need for intervention. Other than radiography, no other investigation is currently available to aid in the diagnosis of TMJ-OA.

Conclusion

Based on the literature review performed, there is a paucity of evidence to definitively identify a common aetiology of end-stage temporomandibular osteoarthritis. More primary research is required to better understand and prevent the need for advanced surgical management of osteoarthritis, particularly in younger populations.

Ethics statement/confirmation of patients' permission

Not applicable.

Authors' contributions

SD was the primary contributor to the data collection, synthesis of results, and completion of the review. GD was involved in study design, editing, and supervision of this research project. All authors reviewed the manuscript prior to publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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[See online]