TEMPOROMANDIBULAR OSTEOARTHRITIS

IN THE YOUNG AND THE ELDERLY

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PREFACE

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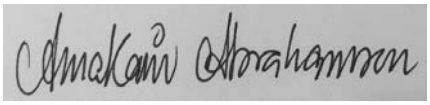
Fredrikstad, September 2019



Anna-Karin Abrahamsson

List of papers

Paper I

Abrahamsson AK, Kristensen M, Arvidsson LZ, Kvien TK, Larheim TA, Haugen IK. Frequency of temporomandibular joint osteoarthritis and related symptoms in a hand osteoarthritis cohort. Osteoarthritis Cartilage. 2017; 25:654-657

Paper II

Ottersen MK, Abrahamsson AK, Larheim TA, Arvidsson LZ. CBCT characteristics and interpretation challenges of temporomandibular joint osteoarthritis in a hand osteoarthritis cohort. Dentomaxillofac Radiol. 2019; 28:20180245

Paper III

Abrahamsson AK, Arvidsson LZ, Småstuen MC, Larheim TA. Repair of bone-destructive temporomandibular joint (TMJ) abnormalities in adolescents with TMJ-related symptoms: A longitudinal study. Dentomaxillofac Radiol. 2019; submitted under revision

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Abbreviations

BMI	Body Mass Index
CT	Computed Tomography
CBCT	Cone Beam Computed Tomography
DC-TMD	Diagnostic Criteria for Temporomandibular Disorder
DICOM	Digital Imaging and Communication in medicine
DDwR	Disc displacement with reduction
DDwoR	Disc displacement without reduction
GCPS	Graded Chronic Pain Scale
INfORM	International Network for Orofacial Pain and Related Disorders Methodology
JFLS	Jaw Functional Limitation Scale
JIA	Juvenile Idiopathic arthritis
MRI	Magnetic Resonance Imaging
NSAID	Nonsteroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorder
TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint

INTRODUCTION

The Temporomandibular joint (TMJ) – some characteristics

During the 8th week of gestation, the temporomandibular joint (TMJ) starts to develop. The joint is one of the last synovial joints to appear in the utero and distinct from other synovial joints, it is formed by 2 separate mesenchymal tissues. Compared to most other joints, the TMJ is relatively immature at birth (1). In childhood, the joint continues to develop as the jaw is used for sucking motion and eventually chewing. The final completion of the joint occurs around the age of 20 (1, 2).

The TMJ is composed of the articular surfaces of the mandibular condyle and the glenoid fossa, the articular disc, the joint capsule and the ligaments. The joint is covered with synovium and filled with synovial fluid (3-5). The TMJ differs from other synovial joints in some ways. It is covered by fibrocartilage (not hyaline cartilage) and its growth center is located superficially under the articular cartilage. From a functional point of view, it is actually two joints (connected by the mandible) that function as one unit, e.g., a bilateral di-arthrodial joint. Together, these joints are responsible for the movement of the mandible. The movement facilitates a broad range of essential life support functions and social interactions, such as production of speech, chewing, swallowing, kissing and mood expressions.

The TMJ is one of the most frequently used joints in the body (6). In addition, it performs a complicated movement (7), including both rotation and translation (a ginglymoid-arthrodial joint). The movement is dictated by associated muscles, limited by ligaments and affected by the morphology of the joint components as well as the dentition (1).

Like other joints, the TMJ can be affected by a number of different diseases and disorders. Temporomandibular disorders (TMDs) is an umbrella term for pain and dysfunction involving the TMJ and its supporting tissues (muscles, tendons). TMD is recognized as a complex disorder with overlapping comorbidities of physical signs and symptoms, as well as changes in behaviors, emotional status, and social interactions as manifestations of general central nervous system dysregulation (8).

Osteoarthritis - definition of the disease

Osteoarthritis (OA) is defined as a degenerative disease that can affect all synovial joints in the body. It is the most common human joint disease and worldwide estimates show that about 10% of men and 18% of women over 60 years have symptomatic OA (9).

OA was long considered a “wear and tear” disease that led to the loss of the cartilage. Research in the last three decades has revealed that the disease is more complex and it is now generally accepted to be an inflammatory and biomechanical disease of the entire joint, not only cartilage (10-12). A new definition of OA was recently endorsed by the OARSI:

“Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness (13, 14).

OA is also the disease that most commonly affects the TMJ (15), and TMJ OA is considered as an important subtype of TMDs (16). Other terms used in the literature to describe TMJ OA, such as arthritis deformans, degenerative arthritis, arthrosis, osteoarthrosis, and degenerative joint disease (5), reflect the long history of both the inflammatory- and the non-inflammatory theories about the disease. However, it is now generally accepted that also TMJ OA is a low-inflammatory “whole joint” disease as in other synovial joints (3, 5, 7).

TMJ OA has the potential to downgrade the TMJ function and thereby reduce the quality of life (5, 7, 17). However, it has been acknowledged that the TMJ has a unique remodeling potential compared to other joints. The regeneration capacity of the mandibular condyle is well known particularly in young individuals, for instance after fracture.

Etiopathogenesis

Both metabolic (local and systemic) and mechanical factors (including genetics) can initiate joint abnormalities that lead to tissue damage and triggers an immune response. If the joint fails to repair or adapt to the damages, the immune cells trigger an inflammatory response with release of inflammatory mediators and activation of the complement system. Gradually, a sustained inflammation develops that cause further destruction of the joint components and results in OA (3, 17).

The molecular mechanisms for this process have been unclear and debated for decades (7). The main reason for this is probably that there is no linear sequence of events that is similar for all individuals with OA. The various etiologic factors that initiate abnormalities, interact with each other and have no common pathologic pathway (10). In addition, the joints response to an abnormality and its adaptive capacity is also influenced by the host (the general condition and genetics), which leads to different biochemical responses in different persons (3, 12). There is increased evidence that the different biochemical responses, and types of inflammation, modulate the clinical and structural presentation of the joints differently (18). In this respect, there is a growing consensus that OA is not a “single disease” of the joints, but rather a “collection of diseases” (or phenotypes) with many causes and different pathologic pathways (10).

As a response to a deeper insight into different biochemical responses and pathologic pathways in OA, a concept of different phenotypes of OA has been introduced in the medical literature (10). OA phenotypes can be defined as subtypes of OA that share distinct underlying pathobiological and pain mechanisms and their structural and functional consequences (19). The underlying idea of this categorization of subtypes, is to improve understanding of the disease and facilitate personalized and individualized prevention and treatment strategies (interventions usually target just one or a few disease mechanisms and may not be equally effective for all phenotypes) (12, 18). However, to understand the root causes of the disease and identify differences and similarities between OA phenotypes is challenging (12). The phenotypes have therefore not fully been characterized (19).

Even though the concept of phenotypes is presented in the TMD literature in connection with pain (20, 21), it seems not to have been established in the TMJ OA literature. However, the

most common factors defining phenotypes are risk or etiologic factors, in addition to genetic variation (22). The risk factors are often mentioned in the TMJ literature. The most mentioned risk factors for TMJ OA, are those who are considered to be potential initiators of tissue damage and alters the joints biomechanics (joint shape, abnormal alignment, unstable occlusion, joint laxity, internal derangements, increased joint friction and more) or those who cause direct tissue damage (macro-trauma, including surgical intervention, or micro-trauma as a result of parafunction). Factors that affect the hosts' general condition (i.e., the response to abnormality and the adaptive capacity) are also often mentioned as risk factors: age, sex (female), genetics, nutritional factors, adiposity, systemic illness (including autoimmune disorders, endocrine disorders, nutritional disorders, metabolic diseases, and infectious disease) or other systemic conditions (generalized osteoarthritis, congenital and developmental abnormalities) (3, 4, 17). The host-adaptive capacity factor, including the general condition, seems to be as important as the initiating factors and may contribute to dysfunctional remodeling of the TMJ, even when the biomechanical stresses are within a normal physiologic range (3).

Epidemiology

Compared to other joints, there is an obvious lack of knowledge about the prevalence of TMJ OA in the general population (23). Most epidemiological studies have investigated subgroups of populations, and patients with TMJ-related symptoms seem to be overrepresented (23). The heterogeneity of the populations, the variations in the diagnostic criteria and the means of assessment of the TMJ (eg. clinical- or radiological signs, based on different modalities) have resulted in frequency estimates with a wide range (17, 23). A recent systematic review where TMJ OA was evaluated both with clinical examination and imaging, found prevalences ranging between 18 and 85 % in patients with TMJ related symptoms (23). TMJ related symptoms that are clinically significant occur in around 5% of the general population (24).

As in other joints with OA, it is found that the incidence of TMJ OA increases with age and is higher among females (25-27). However, it has been speculated that TMJ OA is not as age-related as OA in other joints (7), and a recent CBCT study of younger Korean patients found an almost flat incidence rate throughout the ages from the second decade (28). Due to the fact that the TMJ is relatively immature at birth, it seems to be more susceptible than other joints to perinatal and postnatal insults (1). OA-like lesions in adolescents has been recognized for a

long time (29), and recent radiologic studies have reported frequencies around 10% in asymptomatic individuals and in 27% to 41% in young patients with symptoms and referred for diagnostic imaging (30, 31).

Clinical features

Disease often refers to the abnormalities of the joint components in structure and function. On the other hand, illness refers to the human response to disease, e.g., patient symptoms and disability (a physical or mental impairment that substantially limits life activities). As in other joints with OA, there is still a lack of knowledge about the course of events of TMJ OA, from molecular disease to anatomic disease and to illness (13).

What generally causes patients with OA (in any joint) to visit their family doctor, is pain (that often is worse after weight-bearing activities), morning stiffness and loss of function (32). The signs and symptoms vary in presentation between different patients, which is also consistent in patient with TMJ OA. Painful joints, joint sounds, and reduced jaw function are the most common symptoms that are described for TMJ OA in the literature (4, 5, 17). However, it is difficult to identify and differentiate TMJ OA clinically, since all the TMD diagnoses often share similar signs and symptoms (33), and due to the fact that patients with TMD often have multiple diagnoses. Joint crepitus is the sign that best characterizes TMJ OA (16). However, TMJ OA can also be asymptomatic (4).

The degree of severity of signs and symptoms of TMJ OA can vary considerably from patient to patient and runs from short to prolonged periods of time (34). Among authors, it seems to be a consensus that an acute phase of the disease may be accompanied by morning joint stiffness, joint pain both at rest and at movement, limited mouth opening, crepitus on jaw movements, muscle pain and difficulty in yawning, biting, and chewing. When the disease is arrested to a more adaptable stage, the symptoms decrease or disappear completely (3, 17).

In patients with advanced TMJ OA, malocclusion and facial deformity can be present (3, 4). A posterior bite collapse, premature contacts and an open bite on the contralateral or the affected side can all be a result of the disease process of the bone components. Facial growth disturbances and malocclusion are especially observed and highlighted in young patients with severe osteoarthritic changes (35).

As in other joints with OA, it is common that the disease (often defined by radiologic findings) does not coincide with illness (symptoms). The clinical features may display signs and symptoms of severe disease with no radiologic evidence of joint disorder or vice versa. A weak correlation between symptoms and osseous TMJ findings is usually reported. However, there are still controversies about the correlation (36, 37), and a recent study found that specific bony findings (osteophyte and erosion) may be pain-related variables in TMJ OA (38).

Classification criteria

The diagnosis of OA (in any joint) is most often based on a combination of anamnestic information, clinical examination, and imaging. In a differential diagnostic evaluation, laboratory tests may be obtained. In other joints, a physical examination often confirms joint involvement, and is used to exclude other causes of pain and functional syndromes. Imaging investigations are seldom needed to confirm the diagnosis of OA (but useful to establish the severity of joint damage). However, this is not always the case for the TMJ were clinical examination often underestimates the presence of the disease (16).

A wide range of systems were used for the clinical assessment of the TMDs (Helkimo (39), TMJ scale (40), Craniomandibular index (41)) before the diagnostic protocol RDC-TMD was announced for the research society in 1992 (42). The RDC-TMD aimed to assist the standardization of the assessment, diagnosis, and definition of the most common types of disorders and diseases. Since its publication, it has been the most widely employed diagnostic protocol for TMD research. The RDC-TMD system had a «dual-axis» approach that included an Axis I (evaluating physical findings) and an Axis II (assessing the psychosocial status and pain-related disability) (16). A revised version, named DC-TMD, was published in 2014, with the objective to be feasible for clinicians as well (16). According to DC-TMD, a clinical diagnosis of TMJ OA requires the presence of joint crepitus registered by both examiner and patient. However, the sensitivity for the clinical diagnosis of TMJ OA is low (16). For a reliable diagnosis, imaging is necessary.

Conventional radiography may be useful for osseous evaluation in many joints. In the TMJ, these modalities are unreliable because the bony components are small and superimpositions from the base of the skull often results in a lack of clear delineation (43). Different imaging modalities have therefore been applied to the TMJ over the years, and MRI was for decades

the recommended modality since it is the only method that can visualize both soft tissue and the bone components (44). However, for bone examination, CT is in general accepted as superior to MRI at least regarding bone surface abnormalities, and today CT and CBCT are considered the most reliable methods to assess OA in the TMJ (15, 45).

The typical signs of TMJ OA, as assessed on CT images, were reported early in the 1980s (46). Since that time, imaging criteria have been developed in order to standardize the assessment of the disease. Comprehensive and well-defined image criteria for OA were given by Ahmad et al in 2009 (47), which requires the presence of one or more of the following imaging features for a diagnosis: surface erosion, subcortical cyst, osteophyte, and generalized sclerosis. Although several diagnostic systems still exist in TMJ research, Ahmad's criteria are recommended in the DC-TMD criteria and by INfORM (16).

A great challenge in the assessment of OA (including the TMJ) is that often the disease cannot be diagnosed until it becomes symptomatic, at which point structural alterations already are advanced (32). Due to the limitation of detecting the disease in an early stage, researchers have searched for OA-biomarkers in synovial fluid, serum and urine in the recent years. Although many biochemical markers have been listed as possibly associated with OA, there is no way to detect OA at a molecular level today (7, 14).

In the future, validated objective biomarkers are planned to be incorporated in the DC-TMD in an axis III (16). This together with other assessments of genetics, epigenetics, and neuroscience is believed to improve the diagnostics in the TMD field. Identification of new diagnostic categories, or TMD phenotypes, based on etiologies will most likely occur and put the TMJ OA diagnosis in another perspective.

Management

There is no cure for OA and as the understanding of the complexity of TMD symptoms and the multifactor cause of OA has increased, the use of surgical treatment methods for TMJ OA has become less common. The focus has moved from a “surgery- first” approach towards a more cautious one with non-surgical approach as the primary treatment, then minimally invasive treatments, followed by open surgery when indicated (48).

Non-surgical treatment includes patient awareness and education, jaw exercises, diet modification (soft), behavioral/lifestyle changes, physical therapy, occlusal appliances and short time pharmacotherapy with NSAIDs (or muscle relaxants, antidepressants, antiepileptic agents, and corticosteroids) (4, 7, 18, 48). The treatment aim is to reduce or eliminate inflammation by influencing potential aggravating (risk) factors and thereby facilitating the adaptive process within the joint (48).

While the majority of persons with TMJ OA can be managed with non-surgical treatment methods, there is a small percentage where surgical interventions may be considered. Intra-articular injections (with hyaluronic acid or glucocorticosteroids), arthrocentesis and arthroscopy, are examples of minimally invasive surgical methods (3, 48). Open surgical treatment (also called invasive surgical methods) is reserved for those cases wherein all the previous treatments failed or where the end stage of TMJ OA has created malocclusion or a dentofacial deformity that requires reconstruction. Osseous recontouring, disc repair or removal, condylotomy, orthognathic surgery, and alloplastic total joint reconstruction are interventions that are included in this category (4, 48).

Disease-modifying OA drugs (DMOADs), have been highlighted as promising future therapy (19). This rather new class of drugs aims to target key tissues in the OA pathophysiology process (inhibitors of specific cytokines or specifics cells) and thereby prevent structural progression and symptomatic disease course. Unfortunately, DMOADs have failed in clinical endpoint trials, and it is suggested among other causes, that this is explained by the fact that interventions that target a specific disease mechanism will not be equally effective for all phenotypes (19).

Closing this introduction, there is no doubt that there is a growing knowledge about the multifactor cause of OA and the complexity of TMD symptoms. Presently, the clinical assessment (symptoms, anamnesis, clinical findings, quality of life, etc.) is of most importance when it comes to diagnosis and management of patients with TMJ disease. Imaging offers a potential supplement to the clinical evaluation, since clinical findings may be variable and vague and additional diagnostic information may be needed. Knowledge of bone abnormalities and the dynamics of TMJ OA is therefore fundamental and more knowledge is needed.

The present thesis focuses on TMJ OA in two groups of individuals. The first group is elderly individuals with a diagnosis of hand OA having a general susceptibility for OA. It is often mentioned that polyarticular (generalized) OA is a risk factor for TMJ OA (7, 17), but there are few studies that have investigated TMJ OA in individuals with OA in other joints (discussed in Paper I). The second group is adolescent patients without any known joint disease, but with TMJ related symptoms, signs. It seems to be a diagnostic uncertainty around OA-like abnormalities in young patients (discussed in Paper III), and longitudinal studies are very rare.

Aims

The general aim was to acquire more knowledge about the characteristics of TMJ OA in specific groups; elderly individuals with hand OA and young patients with erosive OA-like abnormalities.

Specific aims

1. Report the frequency of CBCT-defined TMJ OA in a cohort of elderly individuals with hand OA and investigate the reliability of the clinical assessment of TMJ OA in this group (Paper I)

2. Explore the frequency of self-reported TMJ-related symptoms and clinical findings, and their relationship with CBCT-defined TMJ OA in this cohort of elderly individuals (Paper I)

3. Describe the imaging characteristics of TMJ OA in the elderly individuals (Paper II)

4. Investigate the longitudinal changes of the TMJ erosive abnormalities in a group of adolescents with erosive OA-like abnormalities in the TMJ (Paper III)

5. Describe the imaging characteristics at baseline and at follow-up in the group of symptomatic adolescents (Paper III)

6. Investigate the severity of self-reported TMJ-related symptoms at follow-up in the adolescents (Paper III)

MATERIAL AND METHODS

Study design

The present thesis is based on the results of three observational studies. Paper I and II are based on a cross-sectional design that made it possible to investigate TMJ related clinical parameters and TMJ imaging parameters in elderly individuals with hand OA. In paper III, a longitudinal design was used to investigate the radiological development of erosive OA-like abnormalities in adolescents. Cross-sectional analysis of imaging findings (baseline and follow-up) and TMJ related symptoms at follow-up also made it also possible to describe imaging characteristics over time and to explore the severity of follow-up symptoms.

Subjects

The subjects in the thesis belong to two different groups. The first group consists of elderly individuals (non- patients) with OA in the hands, that is with a general susceptibility for OA. These were recruited from a cohort of hand OA patients regardless of whether they had TMJ related symptoms or not. Therefore, these are not named patients but “elderly individuals”. The other group consists of young individuals (patients) that have sought help for their TMJ related symptoms. The group will further be called “young patients”.

Elderly individuals

In Paper I and II, we included 54 elderly individuals from the Oslo hand OA cohort. The individuals had a diagnosis of hand OA and were subject to a clinical and a radiological TMJ examination as a part of the “cohort follow-up” in 2013.

The project was a collaboration between the Department of Maxillofacial Radiology, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo and the Department of Rheumatology, Diakonhjemmet Hospital, Oslo.

The Oslo hand OA cohort was established in 2001. The patients were recruited from the outpatient rheumatology clinic at Diakonhjemmet Hospital and potential study participants were identified by using diagnostic codes in the hospital data system at the Department of Rheumatology. Men and women between 50 and 70 years were eligible for inclusion if they had a diagnosis of hand OA and no other rheumatic diseases. After a thorough review of

patient records of the two years before 2001, 275 eligible patients with clinical Hand OA were identified. The patients with hand OA were contacted by postal mail and 209 patients consented to participate in the baseline examination (2001-03). Follow-up examinations were performed in 2008-2009 and 2013.

At the follow-up examination of 87 patients in 2013, a questionnaire about facial symptoms and a clinical examination of the TMJs and related muscles were included as part of the hand examination protocol at Diakonhjemmet Hospital. Among those, 70 patients voluntarily agreed to have a CBCT TMJ examination at the Department of Maxillofacial Radiology, and 55 patients eventually underwent the examination. One patient was excluded, and therefore the sample in Paper I and II includes 54 of the individuals in the hand OA cohort. A flowchart of the participants that were included in our study is shown in Figure 1.

The majority of the participants were women (n= 48/54, 88%) and the mean (range) age of the participants was 71.3 (61.5-83.0) years. Mean (SD) BMI was 27.6 (6.0).

Young patients

In paper III, we included 22 adolescents with erosive OA-like abnormalities. The patients were initially examined at the Department of Maxillofacial Radiology, University of Oslo, and were selected from the pool of all patients that were referred to the department in the period October 2011 to May 2016 if they met the following criteria: (1) were referred for radiologic examination due to TMJ related pain (pain in the TMJ and/or surrounding structures), (2) <19 years of age, (3) demonstrated erosive TMJ abnormalities at CT/ CBCT. In total, 42 eligible patients were identified. The majority of the patients (their parents if younger than 18 years) were contacted by phone and were invited to participate in a follow-up study. The patients without a registered phone number were contacted by an invitation letter sent to their contact address in the National Population Register. Patients with clinically evident facial growth disturbances or congenital syndromes at baseline were excluded, as well as patients with arthritic disease and those who had had TMJ injection/ surgery or orthognathic surgery before or after the baseline examination. Twenty patients were either excluded, declined to participate, or did not show up for the follow-up examination (Figure 2). The excluded patients were offered an almost identical follow-up consultation (including a voluntary CBCT examination), which three of them completed. Two of the patients that declined had had a recent check of their condition elsewhere).

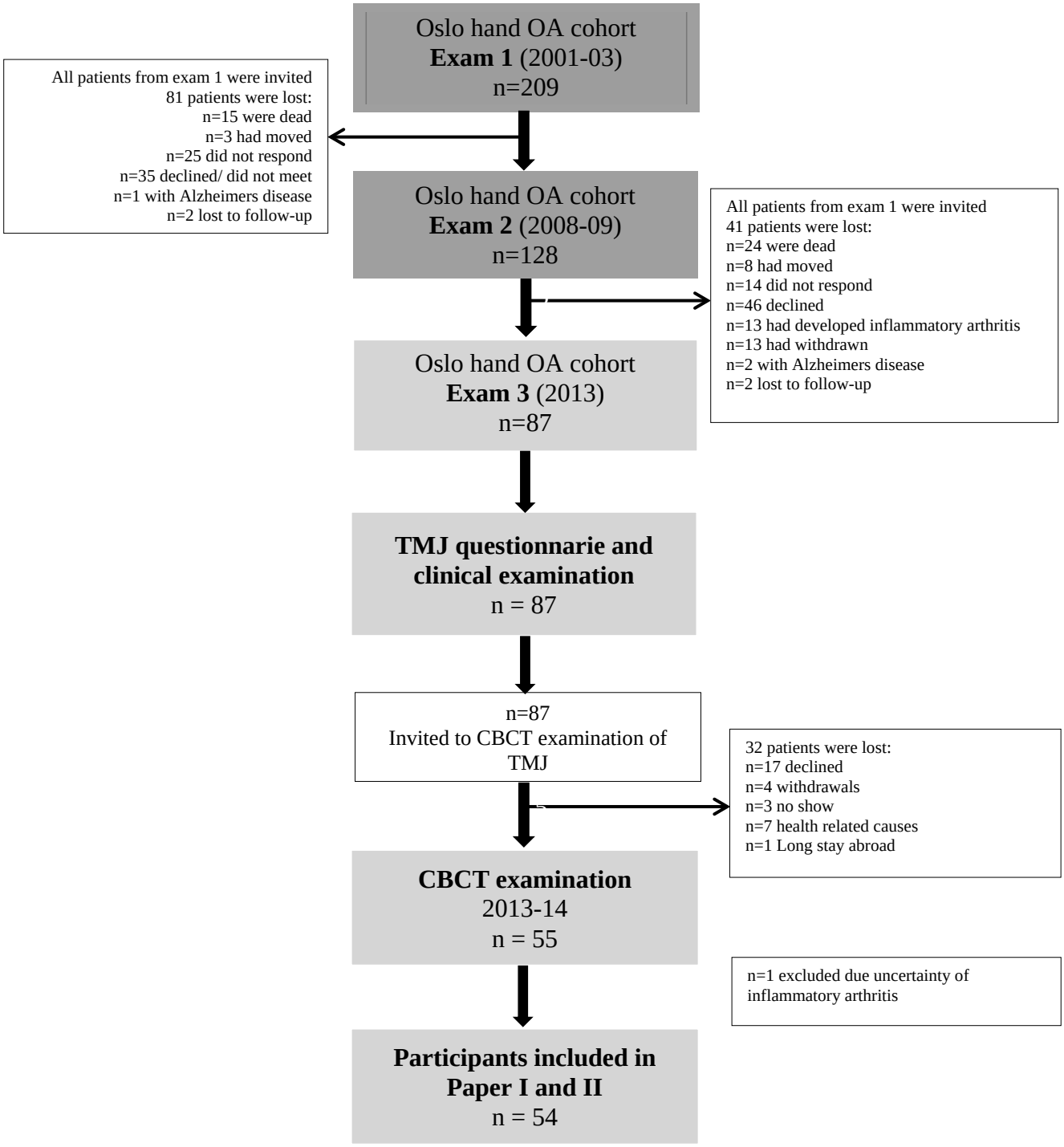

Figure 1. Flow-chart showing the participants in Oslo hand OA cohort included in the TMJ examination (Paper I and II). Modified from Paper I (Supplemental Materials, Figure 1)

The young sample consisted of 21 (95%) females and one male. In baseline, the median age (range) was 16.2 (11.8-18.8) and all participants were students in secondary school or upper secondary school.

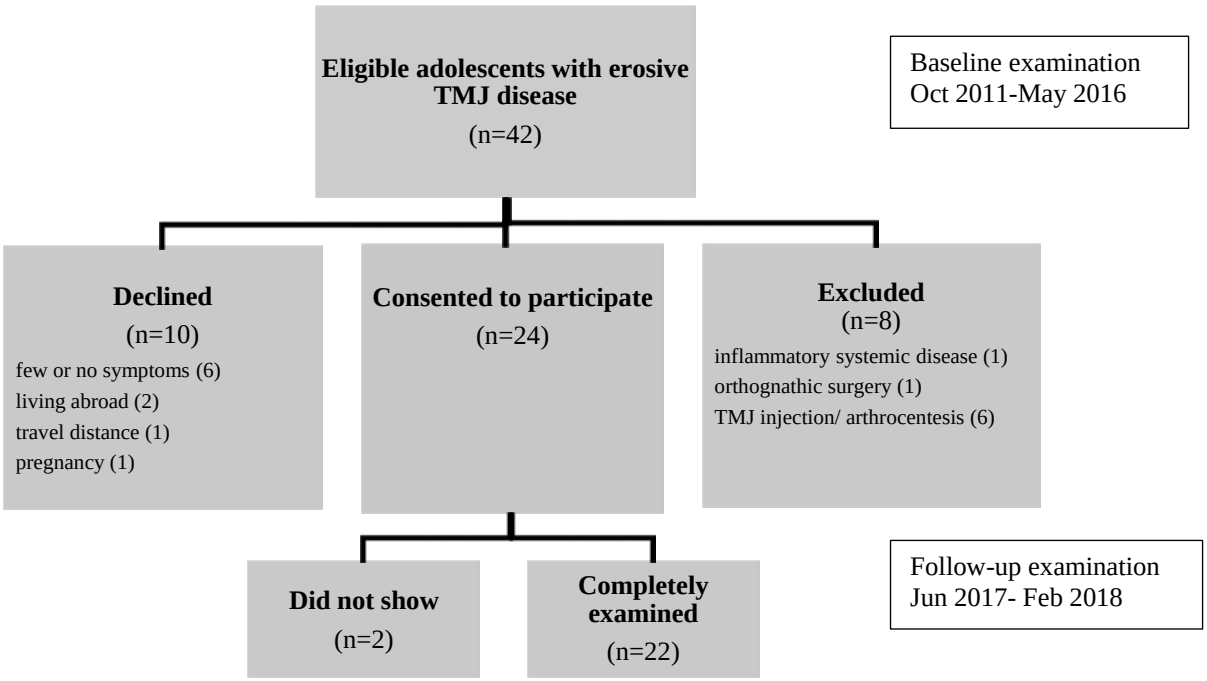

Figure 2. Chart showing the reason for decline or exclusion in paper III.

Data collection

For the elderly individuals (paper I and II), the data collection was performed between June 2013 and March 2014. The clinical assessment consisted of a questionnaire and a clinical examination that was included as part of the hand OA examination protocol at Diakonhjemmet Hospital. The radiological assessment was implemented in another session at the Department of Maxillofacial Radiology (Faculty of Dentistry). A broad spectrum of variables was collected from the elderly individuals in the Oslo Hand OA cohort, including demographic and hand OA related variables. The present thesis reports the TMJ related variables and the most important demographics.

For the young patients (paper III), the follow-up data collection was performed between June 2017 and February 2018. The clinical- (interview and questionnaire) and the radiological assessment were performed in the same session at the Department of Maxillofacial Radiology.

Variables and measurements

Clinical and radiological variables were collected for both the elderly individuals and the young patients. For the elderly individuals, the clinical variables are reported in paper I, while radiological variables mainly are reported in paper II. An overview of the variables used in the analysis in paper I-III is given in Table 1. More detailed explanations of the most important variables are further explained below.

Demographics and covariates

Age and gender were included in all studies. In Paper I and II, the given age in years was the actual age at the clinical assessment. In paper III, the given ages were the actual age at baseline and at follow-up. Follow-up time was calculated by the difference between the dates of baseline and at follow-up examination (paper III).

Table 1. Variables used in the analyses in paper I-III.				
Domain	**Examine**	**Paper I**	**Paper II**	**Paper III**
		Elderly individuals		Young patients
Demographics/ covariates	Age	x	x	x
	Sex	x	x	x
	BMI	x	x	
	Referral reason			x
	Follow-up time			x
Patient reported outcome measures	Author developed questionnaire about symptoms	x		
	GCPS			x
	JFLS-8			x
Physical examination-based measures	Masseter/temporalis muscle pain	x		
	TMJ pain	x		
	TMJ noises	x		
	Maximum unassisted mouth opening	x		
CT/CBCT-based measures	Bone characteristics		x	x
	Radiological diagnosis of OA	x	x	
	Grade of TMJ OA		x	
MRI based measures	Disc position			x
	Grade of disc displacement			x
GCPS; Graded Chronic Pain Scale *JFLS; Jaw Functional Limitation Scale*				

Patient reported outcome measures

Symptom-questionnaire (paper I)

The questionnaire about facial symptoms the last 30 days was included in the booklet of different questionnaires that were used in the hand OA cohort. The patients answered the following questions: the experience of pain (at rest, mouth opening and chewing), the

experience of jaw locking, the experience of noise (clicking or crepitus) on jaw movement and previous contact with the healthcare system due to jaw dysfunction and/or facial pain. The first three questions were not side specific and were answered with “yes”, “no” and “no, but earlier in life”. The last question was answered “yes” or “no”. The questionnaire was developed by the authors based on questions from the RDC/TMD Patient History Questionnaire (49).

Jaw Functional Limitation Scale (paper III)

JFLS assesses the functional status of the masticatory system (50). We used the 8-items version for the last 30 days from DC/TMD (axis II), to measure the global functional limitation of the jaw. In this instrument, eight items related to jaw function during the previous month are rated on a 0-10 scale (i.e., no limitation to severe limitation) and a mean global value is calculated (0-10, high value means more severe limitation). JFSL-8 was scored and interpreted according to the Scoring Manual from DC-TMD (51). Since no cut-offs yet have been provided for the interpretation of JFLS (51), we categorized as follows: (0) no limitation, (1-4) low limitation and (5- >5) significant limitation (52).

Graded Chronic Pain Scale (paper III)

GCPS assesses pain-intensity and pain-related disability (53). We used the 30-day version from DC/TMD (axis II). The GCPS is divided into two parts. The first part assesses pain intensity (0-100, with ≥ 50/100 considered “high intensity”). The second part assesses limitations in physical functioning due to pain. When assessing physical functioning, a disability score (0–6, based on number of days that pain interferes with activity and on extent of interference with social, work, or usual daily activities) is combined with pain intensity (0-100) as follows: Grade 0 = no TMD-pain in the previous month; Grade I = low disability (<3) and low intensity pain (<50); Grade II = low disability (<3) and high intensity pain (>50); Grade III = high disability, moderately limiting (3–4 regardless of pain intensity); Grade IV=high disability, severely limiting (5–6 regardless of pain intensity). High pain and high interference, or moderate to severe disability (Grades III or IV), should be interpreted as disability due to pain and suggests that the individual is experiencing a significant impact from the condition to his or her life. The instrument was scored and interpreted according to the Scoring Manual of the 30-day version from DC-TMD (51).

Physical examination-based measures

One dentist performed the clinical examination according to the Complete specifications (protocol) for DC/TMD (version: 2013) (54) in order to avoid inter-rater bias. The dentist was self-instructed of the DC-TMD protocol, which has shown to almost have the same diagnostic reliability as formal DC/TMD training and calibration (55). The examination included: 1) absence or presence of tenderness upon palpation for M. masseter, M. temporalis and the TMJ, 2) TMJ noises (clicking, crepitus) and 3) maximum unassisted mouth opening. All registrations were side specific. Reduced mouth opening was defined as <40 mm, including vertical overbite. The DC-TMD was used to define clinical TMJ OA, which requires presence of crepitus registered by both examiner and patient (Table 2) (16).

Table 2. Clinical criteria for TMJ OA[1, 2] Indicated history criteria and examination criteria must be met	
History criteria	Positive for at least one of the following: 1. In the last 30 days, any TMJ noise(s) present with jaw movement or function; OR 2. Patient report of any noise present during the examination.
Examination criteria	Positive for the following: 1. Crepitus detected with palpation during at least one of the following: opening, closing, right or left lateral, or protrusive movement(s).
[1] According to the Diagnostic Criteria for Temporomandibular Disorders (16) [2] Nomenclature in Diagnostic Criteria for Temporomandibular Disorders: Degenerative joint disease	

CT/CBCT- based measures

The CBCT examinations were performed at the Department of Maxillofacial Radiology. Different protocols were used in the two samples (Table 3). The CBCT images were taken with teeth in occlusion (intercuspal position) and standardized head position.

Table 3. CBCT protocols		
CBCT protocol	**Elderly individuals** Paper I and II	**Young patients** [1,2] Paper III
CBCT unit	ProMax Mid 3D CBCT (Planmeca Oy, Helsinki, Finland)	3D Morita Accuitomo,XYZ slice Tomograph (J. Morita Corp, Kyoto, Japan)
Tube current	10 mA	7.5-8.0 mA
Voltage	90 kV	85 kV
Rotation	360°	360°
Imaging	Standard	Standard
Field of view (FOV)	200 × 60 mm	140 x 50 mm
Spatial resolution	200 μm.	200 μm
(DAP)	785 mGy/cm^2	1430 - 1640 mGy/cm^2
Scantime	14 s	17.5 s

[1]At follow-up

[2] Baseline examinations were performed with a CT LightSpeed Ultra scanner (GE Medical Systems, Milwaukee, Wis) (120 kVp, 50-90 mA, bone window, spatial resolution 0.625 mm) or a ProMax Mid 3D CBCT unit (Planmeca Oy, Helsinki, Finland) (field of view (FOV) 200 mm X 60mm, 85-95 kVp, 4-10 mA, spatial resolution 0.2-0.5 mm).

Bone characteristics, OA diagnosis

The CT diagnostic criteria by Ahmad et al were used to evaluate the hard tissues (Table 4) (47) . In Paper III, we modified the criteria to suit young, growing joints. In Paper III, the criterion was replaced by (1) “Surface destruction defined as a defect of the articular surface involving the underlying bone and (2) “Surface irregularity”, defined as a minor defect or an irregularity of the articular surface, not involving the underlying bone.

In Paper I, we classified all TMJs as having OA, no OA or to be indeterminate for OA according to the criteria for TMJ OA by Ahmad et al (47) (Table 5). The radiological diagnosis of TMJ OA was used as a reference when we calculated the sensitivity and specificity of the clinical diagnosis of OA.

Table 4. Hard tissue assessment of the CT diagnostic criteria[1] for TMJ OA[2]	
Condylar Hypoplasia	Condylar morphology is normal, but the size is small from all dimensions. This is associated with either an increase in the joint space in a normal articular fossa, or a small articular fossa.
Condylar Hyperplasia	Condylar morphology is normal, but the size is large in all dimensions. This will be associated with either lack of joint
Articular Surface Flattening	A loss of the rounded contour of the surface.
Subcortical Sclerosis	Any increased thickness of the cortical plate in the load bearing areas relative to the adjacent non-load bearing areas.
Subcortical Cyst	A cavity below the articular surface that deviates from normal marrow pattern.
Surface Erosion[3]	Loss of continuity of articular cortex.
Osteophyte	Marginal hypertrophy with sclerotic borders and exophytic angular formation of osseous tissue arising from the surface.
Generalized Sclerosis	No clear trabecular orientation with no delineation between the cortical layer and the trabecular bone that extends throughout the condylar head.
Loose Joint Body	A well-defined calcified structure(s) that is not continuous with the disc or osseous structures of the joint.
Deviation in Form	Condylar deviation in form is defined as a departure from normal shape, such as concavity in the outline of the cortical plate, and not attributable to flattening, erosive changes, osteophytes, hyper or hypoplasia.
Boney Ankylosis	Continuous osseous structure between the condyle and temporal bone associated with no discernable joint space and no translation of the condyle in the open mouth views.
Fossa/eminence	
Articular Surface Flattening	A loss of the rounded contour of the surface.
Subcortical Sclerosis	Any increased thickness of the cortical plate in the load bearing areas relative to the adjacent non-load bearing areas.
Surface Erosion	Loss of continuity of cortical margin.

[1] According to the comprehensive diagnostic criteria by Ahmad et al (47)

[2] Nomenclature in Diagnostic Criteria for Temporomandibular Disorders: Degenerative joint disease (16)

[3] In Paper III, the criterion was replaced by (1) “Surface destruction and (2) “Surface irregularity”

In paper II, we also graded the joints with OA based on the system proposed by Ahmad and Schiffman (45): Grade 1 when the joint displayed either a small osteophyte (<2 mm length), or a single small erosion (<2 mm in depth and width), or a single subcortical cyst (<2 mm in depth and width); Grade 2 when the joint displayed a larger osteophyte (≥2 mm length), and/or a larger erosion (≥2 mm in depth and width), and/or a larger subcortical cyst (≥2 mm in depth and width), and/or two or more imaging signs of Grade l. (paper II) The grading system was published in 2016 (45), but has not been validated.

Table 5. CT criteria[1] for TMJ OA [2]	
No OA	Normal relative size of the condylar head; and No subcortical sclerosis or articular surface flattening; and No deformation due to subcortical cyst, surface erosion, osteophyte or generalized sclerosis.
Indeterminate for OA	Normal relative size of the condylar head; and Subcortical sclerosis with/without articular surface flattening; or Articular surface flattening with/without subcortical sclerosis; and No deformation due to subcortical cyst, surface erosion, osteophyte or generalized sclerosis.
OA	Deformation due to subcortical cyst, surface erosion, osteophyte or generalized sclerosis.
[1] According to the comprehensive diagnostic criteria by Ahmad et al (47) [2] Nomenclature in Diagnostic Criteria for Temporomandibular Disorders: Degenerative joint disease (16)	

In paper III (young patients with growing joints), we classified the joints with erosive findings on the basis of the change of the erosive findings between baseline and follow-up: (A) improvement, (B) no change or (C) worsening. The changes of the erosive findings were evaluated based on the extent of the erosive finding/abnormality and the integrity of the cortical outline.

MRI based measures

In paper III, the MRI of 18/22 young patients were included in the baseline assessment (explained in Paper III). All MRI were performed with a 1.5 T magnet, and in most patients oblique sagittal proton density images were obtained. Fourteen MRI were performed at a one imaging center and four at three other centers.

Disc position and grade of disc displacement

We used the diagnostic criteria by Drace and Enzmann, Ahmad et al and Larheim et al for evaluating the disc position (47, 56, 57). Based on closed and opened mouth MR images, the discs were classified into three categories: normal disc position, DDwR, and DDwoR. The displaced discs were further registered if they were categorized as completely displaced or partially displaced.

Imaging analysis

All CT/ CBCT (Paper I, II and III) and MRI (Paper III) examinations were exported in DICOM format files. All images were analyzed in Sectra PACS viewer IDS five version (Sectra, Linköping, Sweden) on an Eizo Flex Scan GS320 (20 inch, color, 1536 × 2048, 32 bit) monitor. The CT/CBCT mages were reconstructed in axial, oblique sagittal and oblique coronal planes (perpendicular to and parallel with the long axis of the mandibular condyle) in the multiplanar reformatted view of the software. Only PD MRI images were evaluated. The observers were blinded to clinical information and were allowed to adjust the brightness and contrast settings for best display to mimic the routine diagnostic approach.

In paper I and II, all images were interpreted separately by three calibrated maxillofacial radiologists. A second image interpretation of 15 individuals was made after 16 weeks by the three observers for intraobserver agreement analysis. The CBCT examinations for the second interpretation were selected using a random number generator (RNG-Random Number Generator, Intemodino Group s.r.o., App Store). Interobserver disagreement of findings was discussed until consensus was met.

In paper III, the examinations were interpreted separately by two of the calibrated maxillofacial radiologists. The radiologist interpreted all baseline and follow-up examinations

separately and independently. Disagreements between the observers were discussed until consensus was met during a second evaluation, in which baseline and follow-up images were viewed simultaneously. In this session, the radiologists also classified the erosive changes between baseline and follow-up in consensus.

Statistical analysis

The statistical analyses in papers I-III were performed in collaboration with the statisticians Professor, PhD Leiv Sandvik (Paper I and II), and MSc, PhD Milada Cvancarova Småstuen (Paper III). Data analyses were performed using IBM SPSS version 22.0 and 24.0 (Statistical Package for Social Services, Chicago, IL, USA). P-values below a cut-off of 0.05 were considered statistically significant. As our studies were considered exploratory, no correction for multiple testing was made.

In all papers, descriptive statistics were applied to calculate counts and proportions (percentages), mean values, median values, standard deviations (SD), confidence intervals (CI) and maximum and minimum values when appropriate.

Paper I and II

For group comparisons, the independent sample t-test (continuous comparisons) and the chi-square test (categorical variables) were used to compare: (1) demographics and symptoms/ clinical examination findings between non-participants and participants, and (2) demographics between individuals with vs without CBCT defined OA.

Differences in proportions of TMJ related symptoms and clinical examination findings in participants with CBCT-defined TMJ OA vs no/indeterminate for OA were calculated with 95% confidence intervals (CIs) at (paper I).

For reliability studies, kappa statistics analysis was performed by using standard Cohen's kappa (κ) for binary assessment to determine consistency within and between observers (58). Kappa statistics are statistical measures of agreement, or concordance, between raters (interobserver reliability) or among repeated measures by a single rater (intraobserver reliability). It is generally thought to be a more robust measure than simple percent agreement, as kappa takes into account the possibility of the agreement occurring by chance

(59). Our OA ratings were dichotomized as either present (TMJ OA) or absent (no TMJ OA or indeterminate for TMJ OA). For interobserver reliability, the agreement was evaluated pairwise, and a mean of these values gave the final value. Kappa coefficients were interpreted according Fleiss et al (60) κ values of <0.40 are considered to be poor, values from 0.40 to 0.75 to be fair to good, and values >0.75 to be excellent. This will however not be discussed further in this thesis as this is one of the topics for a future thesis on the same material.

The sensitivity and specificity for the clinical diagnosis of OA were calculated using CBCT as reference (Paper I). A tests sensitivity (the proportion of people with the disease who will have a positive test result) and specificity (proportion of people without the disease who will have a negative test result) are a measure of the tests validity which gives information of the test accuracy (i.e. if a test is measuring what it intends to measure).

Paper III

For comparisons of radiological findings at baseline and follow-up, the analyses were performed separately for left and right TMJ. Proportions of patients with erosion at baseline and at follow up were compared with McNemar test to account for dependencies as all patients were assessed twice and these analyses were stratified by side (right or left). When assessing changes in the proportion of patients with type of hard tissue findings (regardless of left or right joints), Wilcoxon signed ranks test was used. Proportions were presented as percentages with 95% confidence intervals (CI) constructed using the binomial distribution approximation.

Legal and ethical aspects

The studies were performed in accordance with the ethical standards of the Helsinki Declaration. Informed consent was obtained from all patients (and their parents if age <16 years). The Regional Ethics Committee of Norway approved the studies (references: 2011/1411 and 2016/1975).

SUMMARY OF RESULTS

Paper I: Frequency of temporomandibular joint osteoarthritis and related symptoms in a hand osteoarthritis cohort

The frequencies of TMJ related symptoms, clinical findings and the diagnostic assessment of TMJ OA by clinical examination or by CBCT, were studied cross-sectionally among 54 elderly (mean (range) age 71.3 (61-83) years) individuals from the Oslo hand OA cohort (Diakonhjemmet Hospital). The frequency of self-reported TMJ symptoms (44%) and clinical findings (93%) was common, but few (13%) of the individuals had sought healthcare for TMJ-related problems. A radiological diagnosis of TMJ OA was found in the majority (67%) of the individuals. One third of those with the disease were bilaterally affected. The individuals with OA reported statistically significantly more pain at mouth opening and joint sounds than individuals without TMJ OA. Normal jaw function capacity was found in all, except one. By clinical examination, only crepitus was more common in individuals with TMJ OA, but the clinical examination (based on the presence of crepitus registered by both examiner and patient) underestimated the frequency of TMJ OA (sensitivity 0.42, specificity 0.93).

The study showed that CBCT-defined TMJ OA was common in patients with hand OA, suggesting that TMJ OA may be part of generalized OA. Few individuals had sought healthcare, despite the high burden of TMJ related symptoms/findings.

Paper II: CBCT characteristics and interpretation challenges of temporomandibular joint osteoarthritis in a hand osteoarthritis cohort

The imaging characteristics (CBCT) of TMJ OA were studied in the material from the Oslo hand OA cohort (2013), where half (49%) of the 108 joints had a diagnosis of TMJ OA. Bone productive changes (osteophyte and sclerosis) in combination with flattening were the most prominent features of TMJ OA in the patients with hand OA. Condylar findings were more frequent than findings in the fossa/eminence, and osteophyte formation of the condyle was the most frequent (72%) radiologic sign decisive for TMJ OA. Osteophyte formation, together with flattening of the condyle and the fossa/eminence was the most frequent combination of findings. Further, large osteophytes (≥ 2 mm) was the main reason that most (68%) of the OA joints was categorized as more severely affected (grade 2). The majority of

the erosive finings (surface erosion and subcortical cysts) were found in the joints with less severe OA (grade 1). Those findings were mostly less prominent and were always seen in combination with the bone-productive features. Interpretation challenges related to subtle changes were identified and were also reflected by the rather low observer agreement. Inter- and intraobserver agreement showed mean values of 0.67 and 0.62, respectively.

The result showed that TMJ OA mostly was characterized by bone productive abnormalities. The radiological features indicated a late-stage TMJ OA in this cohort of elderly individuals with hand OA

Paper III: Repair of bone-destructive temporomandibular joint (TMJ) abnormalities in adolescents with TMJ-related symptoms: A longitudinal study

The longitudinal changes of erosive TMJ abnormalities, the CBCT characteristics at baseline and follow-up and the severity of self-reported follow-up symptoms were studied in 22 patients (baseline median age 16 (12-18) years) with erosive OA-like abnormalities. The median follow-up period was 4.1 (1.3-6.4) years). A significant reduction in the proportion of patients with erosions from baseline to follow-up was found (59.1%, 95% CI [36.4 to 79.3] %). Erosive findings at baseline improved in 9/12 (75%) right and 14/15 (93%) left TMJs. About half of the joints showed repair at follow-up, that is they had developed an intact cortical outline. No significant change was found in the additional hard tissue findings between baseline and follow-up, except for osteophytes that increased significantly (right TMJ p <0.046, left TMJ p < 0.003). The osteophytes were mostly found in joints with erosive findings.

Low or no impairment of the jaw function (JFLS) was found in 12/22 (55%) patients and no or low intensity of pain (GCPS grade 0 or I) in 19/22 (86%).

The study revealed a high potential for repair of erosive TMJ abnormalities in symptomatic adolescents median 4 years after inclusion. At follow-up the majority of patients assessed their symptom severity as low.

DISCUSSION

Methodological considerations

Methodological limitations may contribute to bias and limit the strength of our findings. Bias occurs when systematic errors are introduced into sampling (how the patients are recruited) or testing (i.e., how the data are collected or by using incorrect statistical analyses). The following section will discuss possible limitations in our studies.

Study design and subjects

Paper I and II

The cross-sectional study design in Paper I and II was based on the TMJ examination that was included in the Oslo hand OA cohort (2013). The cohort was a hospital-based, single-center and observational prospective cohort study. A prospective cohort study is the strongest observational study design and suitable for studying predictors and prognostic factors. A cross-sectional study, however, has limited ability to investigate cause and effect but is suitable for studying frequencies. The focus of Paper I and II was therefore to study frequencies of TMJ related symptoms and imaging TMJ characteristics in individuals with hand OA.

For scientific results to be generalized, the study population must represent the general population it aims to investigate (external validity). A possible limitation of a cohort study is when there is a higher likelihood for some members of the population to be included (selection bias due to a non-random sample) which reduces the validity. The hand OA cohort at Diakonhjemmet Hospital consists mainly of patients referred to specialist care and may not be representative for patients with hand OA in general. Further, our result might be biased by the overrepresentation of women in the hand OA cohort. Hand OA may affect both women and men, but symptomatic hand OA seems to be more prevalent in women (61). This might explain why more women than men seek medical care and were more likely recruited to the cohort. The incidence of TMJ OA and TMD are also reported to be more common among females (25, 27, 62). However, although the female/male ratio in our study (paper I and II) was high, similar proportions of men (4/6, 67%) and women (33/49, 65%) were found to have TMJ OA. However, in particular for the men, the series is very small.

Of the 87 patients that participated in the hand OA cohort in 2013, 54 were included in our sample (33 individuals were lost to follow-up). We found no differences in self-reported symptoms and clinical findings between the 54 participants and the 33 non-participants, except for the fact that the non-participants were significantly older than the participants. Health-related causes and the fear of falling in the slippery streets in the hard winter 2014 were some of the reasons that the individuals that initially had consented to participate, changed their mind. This might have been more common in the oldest individuals.

In addition to the diagnosis of hand OA, both age, gender, and BMI were published for the elderly individuals. Several other variables could have been presented (other joints with OA, other diseases, medication, different demographics, etc.) which had characterized our sample better. The results of self-reported health status and use of medication (from the questionnaire), were analyzed but never published (Appendix I). Regarding the health issues results, the participants were mostly affected by blood pressure issues (28%), allergy symptoms (28%) and lung symptoms (asthma, bronchitis or other lung diseases) (19%). The most commonly used medications, previously or presently, were NSAIDs (70%), D-vitamin (63%) and Estrogen (54%).

Paper III

The longitudinal design in the study of young patients (Paper III) was suitable for analyzing the development of erosive hard tissue features in the TMJ. As in all follow-up studies, there is a potential for a loss of patients when the follow-up time is long. This was also our experience, and 12 (29%) patients declined or did not show up to the follow-up. Further, eight patients (19%) were excluded, which resulted in a small sample size that limit the strength of our findings. Whether the non-participants had more or less severe disease (or symptoms) is unknown. Six patients declined due to few or no symptoms. On the other hand, six patients were excluded due to TMJ injection which might indicate that they had a more severe disease or symptoms. Our results can therefore only be generalized to a subgroup of adolescents with erosive TMJ findings who experienced (and sought help for) TMJ-related pain.

To track, contact and arrange a follow-up examination of young people in this age group of globetrotting students was a big challenge in this study. This might be a reason why follow-up studies in this age group are sparse in the literature.

Variables and measurements

A research community benefits from the ability to use well-defined and relevant criteria, and taxonomy to facilitate generalizable research (16). In the last decades, the RDC/TMD (42), which later were replaced by the DC-TMD (16), has been developed to assist the standardization of the assessment, diagnosis, and definition of the most common subtypes of TMD. The DC-TMD criteria were published in 2014, but already in 2012, it was presented to the international clinical research community (16). The timing between the transition from RDC-TMD to DC-TMD (including the choice to use DC-TMD) in our project, unfortunately led to some negative consequences.

First, the DC-TMD protocol was not yet translated and had not been used in a Norwegian population before. The Norwegian translation process (according to INfORM) started in 2013 but was not completed until spring 2019. The clinical examiner commands, in Paper I had therefore been subject to a less comprehensive translation procedure (author translated), which might have resulted in non-comparability of data/diagnoses with those obtained in other languages (63). In Paper III, we used the approved back-translated version of JFLS and GCPS from Jokstad and co-workers (UiT, The Arctic University of Norway).

Second, the DC-TMD (axis I and II) are well validated in adults (16), but validity studies of children and adolescents are sparse and seem not completed (64, 65). In Paper III, we used the instruments JFLS and GCPS from DC-TMD axis II, which have shown acceptable reliability and validity in adults (50, 66). However, in this assessment four of the participants were below 18 years of age. This might limit the strength of our findings. In spite of this, both instruments have been used in young populations and seems to be considered appropriate and adapted for Scandinavian culture (67).

In Paper III, it would have been desirable to have a clinical examination at baseline and follow-up, or at least comparable data of JFLS and GCPS at baseline. However, this was not possible the way the study was designed. Self-perceived symptoms, quality of life and clinical examination findings are of great importance, in particular when it comes to management of a patient. However, to gain a better understanding of the disease process in the TMJ, imaging methods are mandatory.

The CT diagnostic criteria by Ahmad et al (47) are used in all Papers (I-III), which provides an opportunity to compare the CBCT findings of TMJ OA in the elderly individuals and the young patients in this thesis. Even though the CT criteria have been used on adolescents in previous studies (68, 69), they have not been validated. Also, in our opinion, they may not be totally suitable for young TMJs in growth. Our material consisted of joints with different stages of cortical development, making it difficult to apply some of the CT criteria (especially "Surface erosion" defined as a loss of continuity of articular cortex). In Paper III, we therefore modified the criteria. The criterion Surface erosion was replaced by two new criteria (Surface destruction and Surface irregularity) for bone-erosive signs. We also added "beaking", in order to differentiate this feature from an osteophyte (described in Paper III).

To enhance the validity of the CBCT interpretation with the modified criteria, we decided to have two experienced radiologists render consensus diagnoses, rather than depending on a single radiologist. However, the longitudinal changes of erosive findings from baseline to follow-up were assessed using a side by side comparison to mimic a clinical setting, which may introduce bias due to expectation of finding bone changes over time. This method may therefore be less suitable for observational studies (70).

Statistical analyses

From a statistical point of view, the thesis is based on observations from two samples that are relatively small in size. The small samples, especially in Paper III, limited the statistical analyses. Small sample sizes often evoke skepticism about whether the collected data can be subjected to a statistical test, as small studies have limited statistical power and thus can often suffer type II error. In Paper III, we conducted a power calculation of the main outcome and based on those result, we considered our study sufficiently powered. However, our calculated CI intervals (Paper I and III) are wide, and the results must therefore be interpreted with caution.

Our studies raised a common methodological issue, namely the units of analysis for statistical tests. The materials involved measurements from both right and left TMJ in one subject. This will represent a problem, since the data is not independent. A requirement for tests of statistical significance is that the data to be tested are independent. To avoid this problem, we analyzed symptoms/signs vs OA/ non-OA at an individual level (paper I) or performed separate analysis for the left and the right joint (Paper III). A consequence of this is that some

information will be lost (Paper I), and the subgroups becomes small (Paper III). However, in Paper II we presented the radiological TMJ characteristics at joint level without taking account for intra-person dependency (17 individuals (47%) had bilateral signs of OA). In radiological TMJ literature, this type of presentation of radiological characteristics are quite common but may not be the most optimal.

Main results

The imaging characteristics of OA in the TMJ are similar to OA in other joints. In general, the hard tissue findings are often characterized by joint space narrowing, sclerosis, osteophytes and cysts (71). This also applies to the TMJ, but in this joint narrowing of the joint space is an unreliable sign of OA, in particular as the only sign indicating disease (15). But it may be seen – most often in cases of extensive OA (15). Although not typical, erosion may also be a feature of OA in the knees (72), in the hands (73), as well as in the TMJs (47).

The hard tissue findings of OA (as assessed by CT/CBCT) are reported in several articles (25, 26, 31, 37, 38, 68, 74, 75). However, the most frequently found radiological features differ between studies (38). It is often speculated that the contradictory results depends on time, i.e. what phase of the disease the patients are in, and it is proposed that each type of bony feature occurs in different stages of the disease process (3). With the new insight about the heterogeneity of OA pathogenesis, an expanded explanation for the contradictory findings might be that different phenotypes of TMJ OA may have different characteristics. The result of a recent article supports this argument, showing that the structural presentation of TMJ OA was modulated by various types of inflammation and the individual biochemical response of the joints (76). This might indicate that the appearance of the structural (radiological) abnormalities we observe not only are influenced/designed by time, but also by the type of initiating factor (local or systemic), the tissue it affects (cartilage, disc, synovium etc) and the response of the joint tissues which is also dependent on the general condition and genetics of the host.

The main aim in the present thesis was to acquire more knowledge about the imaging characteristics of TMJ OA in two specific groups; elderly individuals with hand OA and adolescents with TMJ related symptoms. Our two groups have different characteristics. What distinguishes them most is age. Age is one of the most known risk factors for OA in general.

Further, the young group consists of TMD patients without any known joint disease, while the elderly are hand OA patients that were investigated independently of whether they had TMJ-related symptoms or not. Thus, in our context they were non-patients. As mentioned earlier, hand OA is considered a marker for a susceptibility of generalized OA, leading to an increased risk for OA in other joints (77).

The hard tissue findings in the elderly individuals (Paper II) were predominantly characterized by bone-productive features. Osteophytes and subcortical sclerosis in the condyle, besides articular flattening, were the most frequent signs. In contrast, erosive features were predominant in the young patients at baseline, and they were often seen in combination with condylar flattening (Paper III). However, in the young individuals with bone abnormalities at follow-up, the hard tissue features had an appearance more similar to the elderly. The combination of both bone-erosive and bone-productive features was common.

Our longitudinal findings in the young individuals are congruent with the proposal of different disease phases of OA (3). The destructive features (erosions) at baseline are associated with an early stage of OA (78). At follow-up, a number of joints with erosions at baseline had no erosions at follow-up. In the remaining joints, a combination of erosive and productive features (osteophytes) were mostly found. These findings are more similar to later stages of TMJ OA, which are mainly characterized by osteophytes as a product of the host's adaptive response according to Hussain et al (78). Whether osteophytes are part of a joint's adaptive response (morphological changes of the structures not associated with any significant alterations in the mechanical function) (79), or should be characterized as degeneration (a maladaptive response where the original tissue is replaced by a tissue structure of inferior quality) (45), can be discussed. According to the hard tissue criteria for TMJ OA, both degeneration and adaption are considered as remodeling processes. However, as in other joints, osteophytes are a determining finding for an OA-diagnosis (45). (Osteophytes are discussed in Paper II and II).

Since the abnormalities of the joint components in TMJ OA may be a result of the insufficient process of adaptation and repair (10), the imaging features may be combined by signs that represent tissue damage, degeneration, and adaptation. Flattening and subcortical sclerosis are often found in joints with OA, but according to the criteria they are signs of remodeling and

are not determining for an OA diagnosis (47). Condylar flattening was common in both our age groups, while sclerosis was a more common finding in the elderly.

The involvement of the fossa/eminence also differed between the groups. In the young individuals, this region had no findings that were determining for OA. In contrast, about 40% of the elderly individuals had fossa/eminence erosions. This number seems high compared to other CBCT studies of TMD patients (<10%) (25, 26, 80). Whether the elderly individuals had a more severe disease, because a longer disease duration or involvement of the fossa /eminence is more typical in patients with general susceptibility for OA (systemic metabolic drivers for the disease), is difficult to determine.

It is often suggested that bilateral involvement of TMJ disease have a more systemic etiology than unilateral. Bilateral TMJ OA were found with a higher frequency in the elderly group (17/36, 47%) compared to the young (baseline 5/22, 23%) (follow-up 5/13, 38%). Since a wide range of frequencies of bilateral TMJ OA are reported in different materials, our proportion of bilateral cases is difficult to interpret. In other joints bilateral involvement is most common in patients with polyarticular (generalized) OA even though a unilateral distribution is also reported (81). Regarding the TMJ, it is reported that OA can be both bilateral and unilateral (17). Bilateral TMJ OA is reported in the range of 60%-70% in patients examined with MRI (82), but a recent longitudinal (repeated cross-sectional) cohort study of a Swedish female population found that the risk for developing TMJ OA in both joints was low (83).

In the conclusion of Paper I, we are suggesting that TMJ OA may be part of generalized OA. The suggestion is based on the frequency of TMJ OA (67%), but since a control group is missing a conclusion cannot be made. As mentioned earlier, the prevalence of TMJ OA in the general population is unknown. However, preliminary result from an ongoing population-based cohort “Oral health of 65-years old Oslo citizens” at the Faculty of Dentistry, University of Oslo, suggests a lower TMJ OA frequency than in our study. In the Oslo population, most of the OA features seem to be of low grade, and erosive findings seem to be more uncommon, compared to the individuals with hand OA. Further, the burden of self-reported symptoms seem low, contrary to the findings in the OA cohort (84).

Different clinical parameters were investigated in our two samples. In the elderly individuals, self- reported symptoms and clinical findings was common, even though those individuals

were non-patients in a TMJ perspective. However, the mouth opening capacity was found to be good, which might be one reason why few had contacted the healthcare system. Regarding the young patients, the majority were referred to our Department due to reduced function or jaw locking problems together with pain in the TMJ and surrounding structures. Unfortunately, self-experienced symptoms (JFLS and GCPS) were not assessed at baseline and could therefore not be compared with the follow-up assessments. Even though about half of the patients had received treatment or performed exercises within the last six months, the impression, was that the symptoms were less pronounced at the follow-up than what they had been at the first visit.

Regarding the erosive OA-like abnormalities in adolescents (Paper III), there is some diagnostic uncertainty that is reflected in the different terminology describing the condition in the TMJ literature (discussed in Paper III). There is little knowledge about the etiology of those abnormalities and validated clinical criteria are missing. In most radiological literature, the erosive abnormalities in adolescents are considered a form of degenerative joint disease (85, 86), but according to articles derived from the International RDC/TMD Consortium group (INfORM) or by the discussion in the Expanding Taxonomy for the DC/TMD, they can also be considered to be part of the diagnostic category TMJ arthritis as a monoarthritic condition (20, 87). The present thesis cannot resolve in what descriptive categories the erosive abnormalities in adolescents should be placed, but it has demonstrated that erosive abnormalities in adolescents can repair (i.e., developing an intact cortical outline) with or without other radiological signs of TMJ OA. It has also demonstrated that the erosive abnormalities can persist over time, and in those cases other signs of TMJ OA (osteophytes) are often present.

CONCLUSIONS

From my research the following conclusions can be drawn:

1. In the hand OA cohort, CBCT-defined TMJ OA was found in as many as two thirds (67%) (Paper I). Clinical examination clearly underestimated the diagnosis of TMJ OA as assessed from CBCT (Paper I) The high frequency found in this study suggests TMJ OA to be part of generalized (polyarticular) OA (Paper I)

2. In the hand OA cohort self-reported TMJ-related symptoms and clinical findings were common. Self-reported pain at mouth opening and joint sounds, in particular crepitus, were significantly more common in individuals with TMJ OA compared to those without (Paper I)

3. In the hand OA cohort, the imaging findings of TMJ OA were characterized by bone-productive features (osteophyte formation and sclerosis) and flattening, indicating a late stage of OA. Large osteophytes were the main reason that most of the OA joints were categorized with the most severe grade of TMJ OA. Destructive findings (surface erosion and subcortical cysts) were less prominent and always seen in combination with bone-productive features (Paper II)

4. In the adolescent group, improvement of the destructive findings was a prominent longitudinal change. About half of the joints with surface destruction developed an intact cortical outline as assessed from CBCT. The reduction in proportion of patients with erosive abnormalities was significant. Worsening of the erosive findings and occurrence of new erosions were uncommon (Paper III)

5. In the adolescent group, the destructive imaging features at baseline in combination with some flattening, indicated an early stage of OA. The imaging features at follow-up were mainly characterized by some flattening but no other bone abnormalities or, by erosive findings together with osteophytes. The follow-up features indicated repair or a later stage of OA.

6. In the adolescent group, the majority assessed their symptom severity as low at follow-up. Low or no limitation of the jaw function was reported in more than half of the patients (Paper III)

Clinical implications

In OA research and patient management, the TMJ is a forgotten joint, similarly as in rheumatic disease research and patient management (88). Patients with OA and other systemic joint diseases are in general managed by rheumatologists. The thesis demonstrated that TMJ-related clinical signs and symptoms were common in individuals with hand OA (Paper I). The findings emphasize the importance for rheumatologists and physicians (general practitioners) to assess TMJ OA and related symptoms in patients with hand OA. Since hand OA often is seen as a marker of generalized (polyarticular) OA, the result may also indicate that TMJ OA can be part of such condition and should not be forgotten in the clinical assessment of those patients. However, the rheumatologists and physicians should be aware that a clinical examination will underestimate the occurrence of TMJ OA. On the other hand, clinical examination will seldom indicate osteoarthritic disease if the joint is healthy (false positive diagnosis).

In Paper III, we demonstrated that improvement of erosive OA-like abnormalities in young patients over time was common and worsening of the erosive findings was rare in our small series of patients. This finding is relevant for the clinician since the literature mostly has focused on the progressive nature of erosive TMJ disease and the management of related facial deformities in adolescents. Treatment of young patients with TMJ related pain is a challenge, and to decide whether the origin of the pain is the masticatory muscles, the joints proper, or a combination may be difficult. If the pain relief is unsatisfactory with non-surgical treatment and the radiological TMJ examination shows destructive signs, there are surgical options that may be considered: primary injection with steroid or another agent or arthrocentesis. Based on the results from Paper III, a follow-up visit to evaluate whether the erosive abnormalities are progressive or reparative is recommended. Complications after TMJ injections have been reported (89, 90).

Future research

At present imaging offers a potential supplement to the clinical evaluation of patients with suspected TMJ OA. Tomography (CT/CBCT) will probably continue to be the cornerstone in an image based TMJ OA diagnosis (when it is indicated) until novel diagnostic opportunities are available. Today, a challenge in the assessment of TMJ OA is that the disease is not diagnosed until structural alterations already are advanced. More work is required on the molecular pathways initiating and perpetuating tissue breakdown, bone remodeling, and inflammation, because knowledge of those pathways may also provide other novel diagnostic (and therapeutic) opportunities.

The future axis III in DC-TMD with validated objective biomarkers and assessment of genetics, epigenetics, and neuroscience seems promising for a better understanding of a complex and multifactorial disease as TMJ OA. Work in those fields is important and imaging in combination with other types of assessments will most probably expand the perspective of TMJ OA. This work will most probably take some time, and until then it is important to develop (improve and validate) the diagnostic assessment tools that already are available. The experience from the present thesis is that there is a need for the instruments in axis I and II to be validated or adapted for adolescents (including establish clinical diagnostic criteria). This also applies to the CT criteria, that in its present form are not suitable for young joints in growth.

Regarding the question, if TMJ OA could be part of a polyarticular (generalized) disease with hand OA as a marker, lager studies are needed (including a control group). Longitudinal studies are warranted to explore whether patients with hand OA are at increased risk of developing TMJ OA. Exploration of the association between TMJ OA and hand OA in a general population could also lead to more clarity of the question.

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APPENDIX I

Self reported[1] health status and use of drugs in the 54 participants in Paper I and II		
Health status[2]	**(n=54)**	**(n=54)**
Blood pressure issues	15	-
Cardiovascular disease (angina, myocardial infarction, other heart failure)	8	-
Lung diseases (asthma, bronchitis, other lung diseases)	10	-
Allergy (hay fever, asthma, eczema)	15	-
Sciatica	3	-
Stroke	2	-
Cancer	4	-
Neurological disease	4	-
Diabetes	6	-
Hypo- or hyperthyroidism	9	-
Mental disorder	3	-
Use of alcohol or other stimulants /drugs/narcotics	1	-
Kidney disorder	3	-
Liver disorder	1	-
Stomach ulcer or other gastric disease	2	-
Blood disorder (anemia or other bleeding disorder)	1	-
Medications[3, 4]		Previously
Prednisolone	10	3
NSAID	13	25
Coxibs	2	16
Methotrexate*	1	1
Antimalaria*	0	3
Etanercept	0	1
Estrogen*	8	21
Bisphosphonates	3	2
Calcitonin	1	0
Calcium	19	5
D-vitamin	27	7

[1] Results from the Oslo Hand OA cohort questionnaire (2013)
[2] Answered “yes” in the questionnaire on the following medical problem at the (question: “Is the patient's health currently affected by one or more of these medical problems?”)
[3] Answered “yes” in the questionnaire on the following medications
[4] No of the participants answered yes for Infliximab, Adalimumab, Rituximab, Abatacept, Auranofin, Sulfasalazine, Myocrisin, Cyclosporine or Leflunomide.
* values were missing for one or two participants
NSAID, Non-steroidal Non-inflammatory Drugs

I

II

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RESEARCH ARTICLE

CBCT characteristics and interpretation challenges of temporomandibular joint osteoarthritis in a hand osteoarthritis cohort

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Objectives: To characterise osteoarthritis (OA) in the temporomandibular joints (TMJs) by means of cone beam CT in a hand OA population, and identify interpretation challenges.
Methods: The TMJs of 54 individuals (mean age 71.3) recruited from the "The Oslo hand OA cohort", independently of TMJ-related symptoms, were examined with cone beam CT (ProMax MidCBCT). Images were analysed for bone change characteristics and each joint was diagnosed with either OA, no OA or as indeterminate for OA. The image analysis criteria developed for the Research Diagnostic Criteria for Temporomandibular Disorders were used. Frequencies of bone changes, joint diagnoses and severity grades (1–2) were calculated, as well as κ values for observer agreement.
Results: In the OA joints, the most frequent bone changes occurred in the condyle: flattening (79%), osteophyte (72%) and subcortical sclerosis (70%). The most frequent changes in the fossa/eminence were flattening (57%), erosion (49%) and subcortical sclerosis (47%). 53 (49%) of the 108 joints were diagnosed with TMJ OA (68 % Grade 2), 29 joints (27%) with no OA, and 26 joints (24%) were indeterminate for OA. Inter- and intraobserver agreement showed mean κ values of 0.67 and 0.62, respectively.
Conclusions: TMJ changes were common in elderly with hand OA and characterised by bone productive changes. The radiologic features indicated a late stage TMJ OA. Interpretation challenges related to subtle changes were identified and are reflected by the rather low observer agreement. The diagnosis of TMJ OA should be based on evident and clear abnormalities only.
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Keywords: temporomandibular joint; diagnostic imaging; osteoarthritis; cone beam computed tomography

Introduction

Osteoarthritis (OA) is the most common joint disease,[1] hence frequently found in the temporomandibular joint (TMJ). It is a complex, gender- and age-related disease with inflammatory mediators released by cartilage, bone and synovium.[2] Severity of the osseous changes increases by age, also in the TMJ.[3] According to Ahmad et al[4] CT is considered the most reliable method to assess OA in the TMJ. Several studies have shown that cone beam CT (CBCT) with lower radiation exposure is similarly accurate, for review see Larheim et al.[5]

In patients with hand OA, an increased susceptibility to develop OA in other joints has been demonstrated.[6] From a cohort of such patients, we recently reported the

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clinical TMJ characteristics in 54 individuals of whom 67% had TMJ OA as diagnosed by means of CBCT.[7] Few studies have explored the CBCT characteristics of TMJ OA in elderly individuals, and we are not aware of any TMJ study in patients with hand OA. Thus, the purpose of the present study was to describe the CBCT characteristics of the TMJs in individuals recruited from this cohort and also to identify interpretation challenges with the diagnostic criteria applied.

Methods and materials

Participants

The present study was performed as a result of a collaboration between the Department of Maxillofacial Radiology, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway and the Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway.

The participants were recruited from the Oslo hand OA cohort, which was established in 2001, consisting of patients with hand OA recruited from the outpatient rheumatology clinic at Diakonhjemmet Hospital. Details of the recruitment and drop-outs, both in Oslo Hand OA cohort and in the present study, have been presented elsewhere.[7–9] Patients included in the present study will be named "individuals" to emphasize that they were not recruited due to TMJ-related symptoms. The study was approved by the Regional Committee of Medical and Health Research (REC) of south-east Norway (2011/1411). Written informed consent was provided by all participants.

Imaging assessment

The CBCT examinations were performed at the Department of Maxillofacial Radiology from august 2013 until March 2014. The CBCT unit was a ProMax Mid 3D CBCT (Planmeca Oy, Helsinki, Finland). Field of view was 200 × 60 mm. Default settings were applied with a voltage of 90 kV and tube current of 10 mA. Spatial resolution on CBCT images was set to 200 μm. CBCT images were taken with teeth in occlusion and standardised head position. Reconstructed images were exported in "digital imaging and communications in medicine" format files. The images were analysed in Sectra PACS viewer IDS five version (Sectra, Linköping, Sweden) on an Eizo Flex Scan GS320 (20 inch, colour, 1536 × 2048, 32 bit) monitor. The images were viewed in axial, oblique sagittal and oblique coronal planes (perpendicular to and parallel with the long axis of the mandibular condyle) in the multiplanar reformatted view of the software. Observers were allowed to adjust the brightness and contrast settings for best display to mimic the routine diagnostic approach. All images were interpreted separately by three maxillofacial radiologists (MKO, LZA, TAL) with 3–30 years of experience of interpreting TMJ images.

Table 1 Osseous diagnosis for the TMJ based on CBCT-defined bone changes[a]

A	No OA	Normal relative size of the condylar head; and No subcortical sclerosis or articular surface flattening; and No deformation due to subcortical cyst, surface erosion, osteophyte or generalised sclerosis.
B	Indeterminate for OA	Normal relative size of the condylar head; and Subcortical sclerosis with/without articular surface flattening; or Articular surface flattening with/without subcortical sclerosis; and No deformation due to subcortical cyst, surface erosion, osteophyte or generalised sclerosis
C	OA	Deformation due to subcortical cyst, surface erosion, osteophyte or generalised sclerosis

CBCT, cone beam CT; OA, osteoarthritis; TMJ, temporomandibular joint.
[a]According to the comprehensive diagnostic criteria by Ahmad et al.[4]

The observers were calibrated before they interpreted all the 54 CBCT examinations independently, blinded to clinical information. The diagnostic criteria described by Ahmad et al[4] were used in the analysis of bone change characteristics, and each TMJ was given a diagnosis of OA, no OA or indeterminate for OA (Table 1).

The TMJ OA were also graded based on the system proposed by Ahmad and Schiffman[10]: Grade 1 when the joint displayed either a small osteophyte (<2 mm length), or a single small erosion (<2 mm in depth and width), or a single small subcortical cyst (<2 mm in depth and width); Grade 2 when the joint displayed a larger osteophyte (≥2 mm length), and/or a larger erosion (≥2 mm in depth and width), and/or a larger subcortical cyst (≥2 mm in depth and width), and/or two or more imaging signs of Grade 1.

A second image interpretation of 15 individuals was made after 16 weeks by the three observers for intraobserver agreement analysis. The CBCT examinations for the second interpretation were selected using a random number generator (RNG-Random Number Generator, Intemodino Group s.r.o., App Store).

Statistical analyses

IBM SPSS v. 25.0 (Statistical Package for Social Services, Chicago, IL) was used for statistical analyses. κ statistics analysis was performed to determine consistency within and between observers. For the reliability studies, OA ratings were dichotomised as either present (TMJ OA) or absent (no TMJ OA or indeterminate for TMJ OA). According to Fleiss et al[11] κ values of <0.40

Table 2 TMJ osseous diagnosis[a] based on CBCT-defined bone changes in 54 individuals recruited from a hand OA cohort

		Patients[7] *n = 54 No. (%)*	*Joints n = 108 No. (%)*
A	No OA	10 (18)	29 (27)
B	Indeterminate for OA	8 (15)	26 (24)
C	OA	36 (67)	53 (49)

CBCT, cone beam CT; OA, osteoarthritis; TMJ, temporomandibular joint.
[a]According to the comprehensive diagnostic criteria by Ahmad et al.[4]

are considered to be poor, values from 0.40 to 0.75 to be fair to good, and values >0.75 to be excellent. For interobserver reliability, the agreement was evaluated pairwise, and a mean of these values gave the final κ value. Any disagreement between the observers was discussed until consensus was met and each joint got a final imaging diagnosis.

Results

A total of 54 individuals were included in the present study (48 females and 6 males). The mean age was 71.3 years ± 5.2 (SD) (range, 61–83 years).

53 (49%) of the total series of 108 joints were found to have OA. The remaining 55 joints were either normal or interpreted as indeterminate for OA (Table 2).

In the 53 TMJs diagnosed with OA, articular surface flattening (79%), osteophyte (72%) and subcortical sclerosis (70%) were the most frequent changes in the condyle. The most frequent changes in the fossa/eminence were flattening (57%), followed by surface erosion (49%) and subcortical sclerosis (47%) (Table 3).

36 (68%) of the 53 OA joints were categorised as Grade 2, and the remaining 17 (32%) as Grade 1. Osteophyte ≥ 2 mm was found in 22 (61%) Grade 2 joints. All findings of cortical erosions and subcortical cysts in the OA joints were measured <2 mm in both depth and width, and the diagnoses of the remaining 39% of Grade 2 joints were based on the findings of two or more imaging signs of Grade 1.

The most frequent combination of bone changes in TMJ OA was articular surface flattening and osteophyte formation of the condyle, together with flattening of the fossa/eminence (Figure 1). Combinations of at least these three bone changes were seen in 28 (53%) of the 53 joints with OA. Another frequent combination was articular surface flattening and osteophyte in the condyle, together with surface erosion in the fossa/eminence (Figure 2). Combinations of at least these three bone changes were seen in 19 (36 %) of the 53 joints with OA.

In the 26 joints interpreted as indeterminate for OA, 14 had articular surface flattening, 7 had subcortical sclerosis, and 5 had a combination of both subcortical sclerosis and surface flattening.

Table 3 Frequencies of CBCT-defined bone changes[a] in TMJs with OA

Bone changes	*OA joints n = 53 No. (%)*
Condylar head	
Articular surface flattening	42 (79)
Osteophyte	38 (72)
Subcortical sclerosis	37 (70)
Surface erosion	21 (40)
Subcortical cyst	8 (15)
Deviation in form	4 (8)
Loose calcified body	3 (6)
Generalised sclerosis	2 (4)
Condylar hypoplasia	2 (4)
Condylar hyperplasia	0
Bony ankylosis	0
Fossa/eminence	
Articular surface flattening	30 (57)
Surface erosion	26 (49)
Subcortical sclerosis	25 (47)
Subcortical cyst	2 (4)

CBCT, cone beam CT; OA, osteoarthritis; TMJ, temporomandibular joint.
[a]According to the comprehensive diagnostic criteria by Ahmad et al.[4]

Inter- and intraobserver agreement for the imaging assessment showed mean κ values of 0.67 (range 0.61–0.74) and 0.62 (range 0.54–0.66), respectively. When excluding the registrations of the least experienced observer, the corresponding mean κ values were 0.61 and 0.65, respectively.

Discussion

This is the first report demonstrating the CBCT characteristics of TMJ OA in a study population of elderly with hand OA. Although the individuals were recruited regardless of TMJ-related symptoms, half of the joints proved to have OA. Typically, more than one imaging sign was present, and a combination of at least three signs was seen in more than half of the OA joints. Articular surface flattening, osteophytes and subcortical sclerosis in the condyle were the most frequent signs. Thus, the imaging features were mainly characterised by bone productive changes. Since surface flattening and subcortical sclerosis are both considered indeterminate for the diagnosis, osteophyte formation was clearly the most frequent of the radiologic signs decisive for OA. This feature was evident in more than two-thirds of the OA joints (Figure 1). Surface erosions occurred consistently as small cortical irregularities (<2 mm in depth and width) and not as punched-out erosions. Both surface erosions and subcortical cysts were always seen in combination with bone productive changes. We therefore consider the radiologic features to represent a late stage of TMJ OA in accordance with previous studies, as reviewed by Hussain et al.[12] They also discussed that

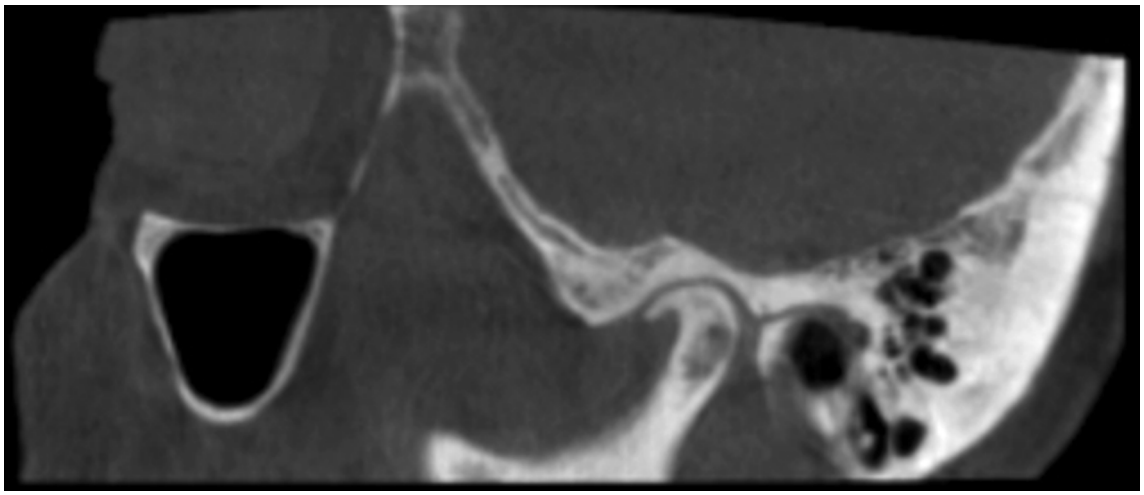

Figure 1 Female, 77 years. Oblique sagittal CBCT view shows deformed joint with condylar osteophyte and subcortical sclerosis in condyle and fossa, interpreted as osteoarthritis. CBCT, cone beam CT.

osteophytes are formed to stabilise the TMJ by repairing and broadening the joint surfaces, as shown in other joints.

The impression of a quiescent late stage of TMJ OA in the present study population was supported by clinical observations such as normal mouth opening capacity, and by the fact that only a minority had sought healthcare due to TMJ-related symptoms.[7] Clinical symptoms of TMJ OA seem to resolve after some time, except for crepitus,[13] which is consistent with the findings in the present study population.[7]

Considering the increased susceptibility of patients with hand OA to develop OA in other joints,[6] the frequency of TMJ OA in this population is expected to be high. Since no study in the general elderly population seems to be available for comparison, the figure of 67% is difficult to interpret. In a CT study of patients with generalised OA and symptomatic TMJs, 80% showed TMJ OA[14] although the mean age (63 years) was lower compared to our study group (71 years). In a population-based MRI study of a birth cohort (mean age 74.6 years) the frequency was 70%.[15] Due to differences in method and study population, the frequencies should be compared with caution. Another reason for this is the use of different diagnostic criteria. In both studies, the authors considered subcortical sclerosis as a sign decisive for OA,[14,15] in one of them also surface flattening.[15] According to Ahmad et al,[4] we did not consider subcortical sclerosis and surface flattening to be decisive for TMJ OA.

Even with the same diagnostic criteria[4] and the same imaging modality (CBCT), a substantial variation of TMJ OA frequencies, from 25.0 to 79.8% of joints, have been reported in asymptomatic individuals.[16,17] To some extent this can be explained by differences in study populations. The interpretation of image signs may also

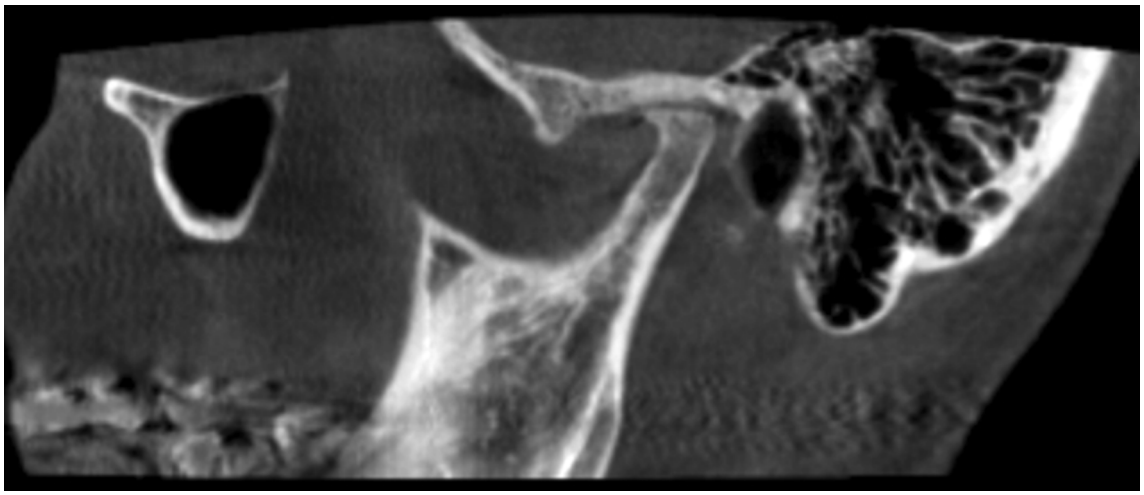

Figure 2 Female, 72 years. Oblique sagittal CBCT view shows deformed joint with surface flattening of condyle and fossa/ eminence, surface erosion and subcortical sclerosis in the fossa, interpreted as osteoarthritis. CBCT, cone beam CT.

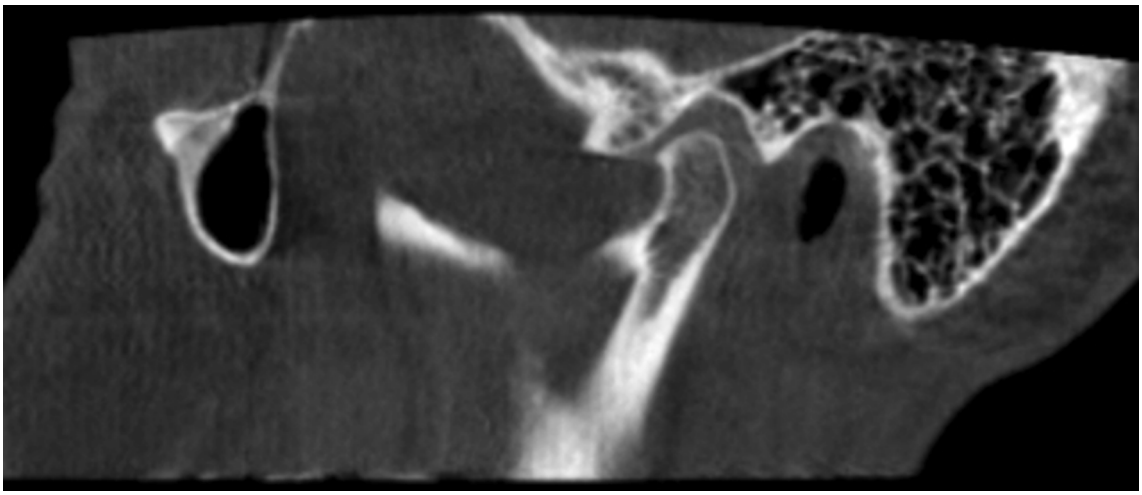

Figure 3 Female, 69 years. Oblique sagittal CBCT view shows small beaking of the anterior aspect of the condyle due to the close position of the cortical plates, interpreted as no osteoarthritis. CBCT, cone beam CT.

lead to different diagnostic results in different studies, but interpretation challenges are rarely discussed in TMJ diagnostic studies.

One specific challenge in the present study was the interpretation of a subtle beaking of the anterior aspect of the condyle *vs* a frank osteophyte (Figure 1). A flattening of the anterior slope and a pointed anterior tip of a condyle might be interpreted as an osteophyte. Assessing the presence of subcortical sclerosis/sclerotic border, which is decisive for an osteophyte according to the criteria, was the major challenge in those cases. However, in the anterior portion of the condyle, mild sclerosis can in some cases be almost impossible to differentiate from "impression of sclerosis", which may occur due to the close position of the cortical plates.[18] In our opinion, an exophytic angular formation, if very small (<1 mm) and observed as the only sign, should not be decisive for an OA diagnosis (Figure 3).Small osteophyte-like formations have been reported in asymptomatic individuals.[19,20]

Another specific challenge was the interpretation of sclerosis, which may vary considerably, from just a slightly thickened cortical plate, to a generalised sclerosis. Various degrees of sclerosis are also typical in other joints with OA.[21] We found it particularly challenging to differentiate between subcortical sclerosis, defined as "any increased thickness of the cortical plate", and generalised sclerosis, defined as "no clear trabecular orientation with no delineation between the cortical layer and the trabecular bone that extends throughout the condylar head". This differentiation is of great importance, because generalised sclerosis is decisive for OA, while subcortical sclerosis is not. We reported generalised sclerosis in only two joints. The very small number might be explained by our interpretation of the criterion. It is unclear to us how extensive a sclerosis needs to be to be classified as generalised, *i.e.* "extending throughout the condylar head".[4]

In the present study, a high number of joints were categorised as "indeterminate for OA". This is in accordance with other studies using the same criteria.[16,22] Uncertain diagnosis should be kept to a minimum in any diagnostic classification system. If only the joints with combined flattening and sclerosis had been included (Figure 4), the category "indeterminate for OA" would have dropped from 24% to about 5% in the present study population. Slight flattening could be interpreted as a normal variant. This finding is reported in one-third of TMJs in healthy adults, and is not considered a reliable indicator for OA in other joints.[23] Similarly, subcortical sclerosis, when occurring alone, could be a normal variant. However, the question is how pronounced the changes must be to be classified as disease. According to Ahmad and Schiffman,[10] flattening and sclerosis may progress to OA representing regressive remodelling, whereas non-progression would represent adaptive remodelling. Exploring flattening and sclerosis as precursors for OA development requires longitudinal follow-up of TMJs categorised as indeterminate.

Observer interpretation disagreement resulted in κ values lower than those obtained by Ahmad et al[4] although being fair to good according to Fleiss et al.[11] In the present study, there was a substantial variation in experience between the observers. Even when excluding the registrations of the least experienced observer the values were rather low. Subtle findings, challenging the differentiation between pathology and normal anatomy, were usually the cause of disagreement in interpretation. In a recent review, we emphasized that the diagnosis of OA should be based on evident, and not on subtle bone changes that may represent a normal anatomic variation or remodelling.[24] The experience from the present investigation fully support this view. Subtle bone changes are unreliable and can lead to overdiagnosis if classified as pathology.

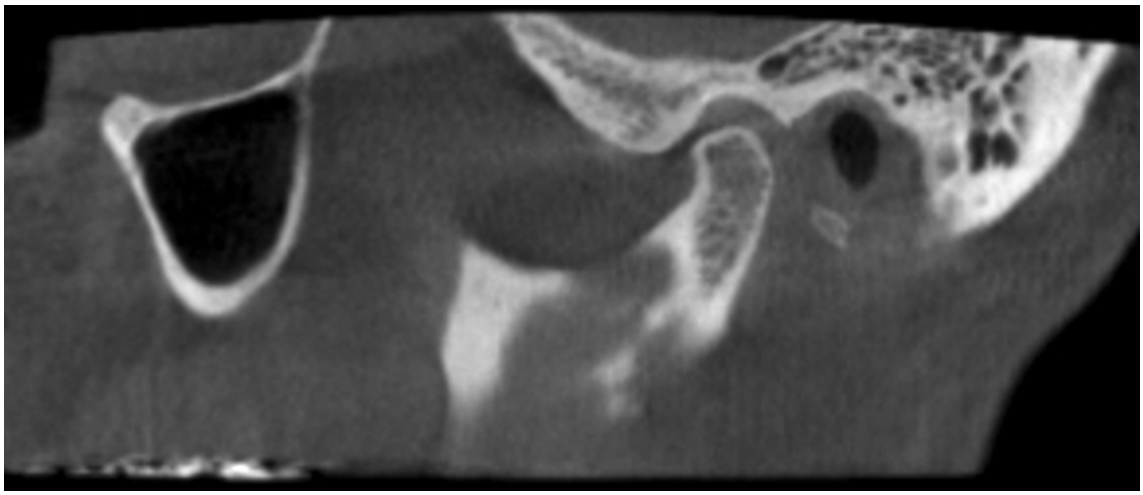

Figure 4 Female, 66. Oblique sagittal CBCT view shows condylar flattening and sclerosis in the fossa/ eminence area, interpreted as indeterminate for osteoarthritis. CBCT, cone beam CT.

The present study has some limitations. The sample size is relatively small. A larger sample size and a control group would have strengthened the reliability of the current study results. It also has to be emphasized that, to our knowledge, the grading system of OA in the TMJ proposed by Ahmad and Schiffman[10] has not been validated.

Conclusions

TMJ OA was common in elderly individuals with hand OA and characterised by bone productive changes, indicating a late stage of disease. Interpretation challenges related to subtle changes were identified and are reflected by the rather low observer agreement. The diagnosis of TMJ OA should be based on evident and clear abnormalities only.

Acknowledgment

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III

Repair of bone-destructive temporomandibular joint (TMJ) abnormalities in adolescents with TMJ-related symptoms: A longitudinal study

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ABSTRACT

Objectives: To investigate longitudinal changes of erosive temporomandibular joint (TMJ) abnormalities in symptomatic adolescents. Secondary aims were to investigate a) imaging characteristics at baseline and follow-up and b) severity of self-reported symptoms at follow-up.

Methods: A cone beam computed tomography (CBCT)/CT follow-up examination (median follow-up 4.1 (1.3-6.4) years) was performed in 22 patients with TMJ erosions (baseline median age 16 (12-18) years). Imaging characteristics were analyzed and changes of the erosive findings between the examinations were categorized as (A) improvement, (B) no change, or (C) worsening. Severity of follow-up symptoms was evaluated using Jaw Functional Limitation Scale (JFLS-8) and Graded Chronic Pain Scale (GCPS) (grade 0-IV). Analyses were performed separately for left and right TMJ. Findings at baseline and follow-up were compared using McNemar test to account for dependencies. Changes in proportions of hard tissue findings between examinations were assessed using Wilcoxon signed ranks test.

Results: A significant reduction in the proportion of patients with erosion was found (59.1%, 95%CI [36.4 -79.3] %) between baseline and follow-up. Baseline erosions improved in 9/12 (75%) right and 14/15 (93%) left TMJs. About half repaired; developed an intact cortical outline. Number of joint with osteophytes increased (right ($p<0.04$), left ($p< 0.003$), mostly in joints with erosive findings. Low or no limitation of jaw function (JFLS) was found in 12/22 (55%) and no or low intensity of pain (GCPS grade 0 or I) in 19/22 (86%).

Conclusion: Our longitudinal study revealed a high potential for repair of TMJ erosions, however, the patient series was small. The majority of patients assessed their symptom severity as low at follow-up.

Keywords: Temporomandibular Joint (TMJ), diagnostic imaging, osteoarthritis, Cone-Beam Computed Tomography (CBCT), adolescents.

INTRODUCTION

Osteoarthritis (OA) like abnormalities of the temporomandibular joint (TMJ) in adolescents have been recognized for a long time. In recent years, frequencies ranging from 27%-41% have been reported in individuals with TMJ-related symptoms referred for diagnostic imaging (1, 2).

Such abnormalities, whether they represent one entity with different forms of severity or different entities, may be characterized by bone-destructive imaging features (2-5). Destructive TMJ abnormalities in young patients should be taken seriously. They might represent a progressive condition such as idiopathic condylar resorption or juvenile idiopathic arthritis (5, 6). The literature has almost entirely focused on the progressive nature of such abnormalities, and the management of the related facial deformities that may occur. Surgical interventions with injections have also been performed, in particular on adolescents with JIA (7). However, longitudinal studies that demonstrate progressive bone-destructive TMJ changes are scarce.

Evaluation of the bony structures in young, growing individuals is challenging. The condylar surface may have a delicate cortical outline, being partially present or, in early age, not present at all (8). Computed tomography (CT) or cone beam CT (CBCT) are accepted as the most reliable methods to assess the bony articular surfaces of this joint (9, 10). CT proved to be superior to magnetic resonance imaging (MRI) in a comprehensive study on adults (9). CBCT is preferable since the diagnostic accuracy is similar and the radiation exposure is lower compared to CT (10). However, ionizing radiation should be used with caution in the examination of young individuals. Most patients with TMJ-related symptoms have myalgia, for which imaging is unnecessary, and disc displacement (11). When diagnostic imaging of

the TMJ is needed, MRI is generally accepted as the method of choice. However, MRI and CBCT are methods supplementing each other regarding diagnostic information yield. In elderly people with a more frequent occurrence of OA, CBCT may be the primary method (12).

We conducted a longitudinal study of symptomatic adolescents with TMJ-related symptoms and bone-destructive TMJ abnormalities, without evident facial deformities. The main aim was to investigate the longitudinal changes of the TMJ destruction median 4 years after baseline (first visit). Secondary aims were to study (a) the imaging characteristics at baseline and follow-up (second visit) and (b) the severity of the TMJ-related patient symptoms at follow-up.

MATERIAL AND METHODS

This observational study was approved by the Regional Ethics Committee of Norway (reference 2016/1975). Written informed consent was provided by the participants, or by their parents when younger than 16 years.

All participants had initially been referred to, and were examined at the Department of Maxillofacial Radiology, University of Oslo in the period October 2011 to May 2016. They were selected if they met the following criteria: (1) were referred for radiological examination due to TMJ-related pain (pain in the TMJ and/or surrounding structures), (2) were younger than 19 years of age, (3) demonstrated bone-destructive TMJ abnormalities at CT/ CBCT. In total, 42 eligible patients were identified and invited to participate in a follow-up examination. Exclusion criteria were: clinically evident facial growth disturbances (micrognathia or facial asymmetry) registered at the baseline, congenital syndromes, and arthritic disease. Patients who had had TMJ injection or surgery, or orthognathic surgery before or after the baseline

examination, were also excluded. Twenty patients were either excluded, declined to participate, or did not show up at the follow-up (Figure 1). The final sample comprised of 22 adolescents (44 joints).

Clinical recordings and interview

Indications for the radiological examination of each participant at baseline were retrieved from clinical records. In the follow-up assessment the participants were interviewed about previous management of their TMJ-related symptoms (counselling, masticatory muscle exercises, occlusal appliance, analgesics, physical therapy, acupuncture, intramuscular injections with botulinum toxin, cognitive therapy, general relaxation exercises or others) (yes/no), TMJ-related treatment the previous six months (yes/no), as well as symptoms from other joints (pain/swelling/reduced movement) (yes/no). Previous traumas against jaw or face/head (yes/no, before/after baseline examination), were also recorded.

Questionnaires

For the follow-up assessment, the Norwegian versions of Jaw Functional Limitation Scale (JFLS-8) and Graded Chronic Pain Scale (GCPS) from Diagnostic Criteria for Temporomandibular Disorder (DC/TMD) axis II were used to map the functional status of the masticatory system, and the pain-intensity and disability status. The JFLS-8 was used to assess global jaw functional limitation of the masticatory system (13). Eight items related to jaw function during the previous month were rated on a 0-10 scale (no limitation to severe limitation) and a mean value was calculated. The scores were categorized as follows: (0) no limitation, (1-4) low limitation and (5- >5) significant limitation (14). The GCPS severity scale was used to assess pain-intensity and disability (15). Seven questions concerning pain intensity, interference with activities and disability days yielded a 0-IV scale score. Grade 0

was defined as no TMD pain, grade I as TMD pain of low-intensity and grade II as high-intensity pain. Grades III and IV reflected moderate to significant pain-related psychosocial disability regardless of pain level (15, 16). JFLS-8 and GCPS were scored and interpreted according to the Scoring Manual from the RDC-TMD international (17).

Imaging

At the baseline visit, the 22 patients had been examined with CT or CBCT. At the follow-up examination, only CBCT was used. The clinical routine for young patients with bone-destructive findings also included a referral for an MR examination of the TMJs. Recently performed MRIs were retrieved. Due to practical reasons and limited access to MRI facilities, examinations from 18 patients were collected.

The baseline examinations were performed with a CT LightSpeed Ultra scanner (GE Medical Systems, Milwaukee, Wis) (120 kVp, 50-90 mA, bone window, spatial resolution 0.625 mm) or a ProMax Mid 3D CBCT unit (Planmeca Oy, Helsinki, Finland) (field of view (FOV) 200 mm X 60mm, 85-95 kVp, 4-10 mA, spatial resolution 0.2-0.5 mm).

The MR examinations were performed with a 1.5 T magnet. Oblique sagittal proton images were obtained to evaluate the disc position at closed and open mouth. The MRI examination of one joint was excluded due to suboptimal image quality; leaving 35 joints for analysis. The MRI examinations were performed with a median time of 21 days after the CT/CBCT examination at baseline (between 97 days before, and 384 days after). Seven patients had MRI within 3 days after the CBCT examination and 4 patients had more than 100 days between the examinations.

The follow-up examinations were performed with a CBCT machine; 3D Morita Accuitomo, XYZ slice Tomograph (J. Morita Corp, Kyoto, Japan) (FOV 140mm X 50mm, 85 kVp, 7.5 or 8 mA, spatial resolution 0.2 mm). All examinations were performed at the Department of Maxillofacial Radiology, University of Oslo.

Image analysis

Reconstructed (baseline and follow-up) images in axial, oblique sagittal and oblique coronal planes were analysed in Sectra PACS viewer IDS 7 version (Sectra, Linköping, Sweden) on Eizo FlexScan GS320 (20-inch, color, 1536 x2048, 32 bit) monitors. The examinations were interpreted by two maxillofacial radiologists (LZA, TAL), with more than 15 years' and 40 years' experience of interpreting TMJ images.

The CT diagnostic criteria by Ahmad et al were used to evaluate the hard tissues (9). Author based criteria for evaluating bone destruction or erosion in growing joints were developed: (1) "Surface destruction", defined as a defect of the articular surface involving the underlying bone and (2) "Surface irregularity", defined as a minor defect or an irregularity of the articular surface, not involving the underlying bone. We also added "beaking" and defined this feature as an angular formation on the anterior aspect of the condyle without presence of subcortical sclerosis, in order to differentiate this feature from an osteophyte with presence of subcortical sclerosis.

For evaluation of the disc position, the diagnostic criteria by Drace and Enzmann, Ahmad et al and Larheim et al were used (9, 18, 19). The position of the disc was determined in all sections throughout the joint on closed and opened mouth MRI and classified into three categories: normal disc position, anterior disc displacement with reduction (DDwR), and anterior disc displacement without reduction (DDwoR). A disc was defined as anteriorly

displaced at closed mouth in the oblique sagittal plane when, relative to the superior aspect of the condyle, the border between the low signal of the disc and the high signal of the retrodiscal tissue was located anterior to the 11:30 clock position (9, 18). A disc displaced in all sections through the joint was defined as completely displaced (19). A disc located with its intermediate zone or posterior band caudally to the apex of the articular eminence at closed mouth, was defined as severely displaced. All severely displaced discs were non-reducing. Therefore, a few joints with severe disc displacement on closed mouth MRI, but without good definition of the disc on open mouth MRI, were also categorized as non-reducing (DDwoR).

After calibration, each radiologist interpreted all baseline and follow-up examinations separately and independently. They were blinded to clinical information except for age and could adjust the brightness and contrast settings for best display. Disagreements between the observers were discussed until consensus was met during a second evaluation, in which baseline and follow-up images were viewed simultaneously. In this session, the radiologists in consensus also classified each joint, based on the erosive changes between baseline and follow-up, in three categories: (A) improvement (B) no change or (C) worsening. The longitudinal changes of the erosive findings were evaluated based on the extent of the erosive finding/abnormality and the integrity of the cortical outline. Improvement was defined as a decrease in the extent of the erosive findings and/or a more intact cortical outline/articular surface. Repair was defined as a completion of the corticated outline. Worsening was defined as an increase in the extent of the erosive findings and/or a less intact cortical outline/articular surface.

Statistical analyses

Data were described as counts and proportions (percentages) for categorical data and mean with standard deviation (SD) or median with range for continuous variables when appropriate. Analyses were performed separately for left and right TMJ.

Proportions of patients with erosive findings (surface destruction and surface irregularity) at baseline and at follow-up were compared with McNemar test to account for dependencies as all patients were assessed twice and these analyses were stratified by side (right or left). When assessing changes in the proportion of patients with different types of hard tissue findings (regardless of left or right joints), Wilcoxon signed ranks test was used.

Proportions were presented as percentages with 95% confidence intervals (CI) constructed using the binomial distribution approximation. P-values <0.05 were considered statistically significant. As our study was considered exploratory, no correction for multiple testing was made. Analysis was preformed using IBM SPSS version 24.0 (Statistical Package for Social Services, Chicago, IL, USA).

RESULTS

Twenty-one females and one male were included in the present study and the median (range) follow-up time was 4.1 (1.3-6.4) years. The median age (range) was 16.2 (11.8-18.8) years at baseline and 20.6 (13.2-23.5) years at follow-up.

The indications for radiological examination at baseline were: pain in TMJ and/or surrounding structures 4/22 (18 %), pain and reduced jaw function 10/22 (45 %) and pain and jaw locking problems 8/22 (37 %).

Clinical recordings and interview

Previous TMJ-related management was reported by 21/22 (95%) patients: counselling 21/22 (95%), masticatory muscle exercises 18/22 (82%), occlusal appliance 16/22 (73%), analgesics

12/22 (55%), physical treatment 8/22 (36%) and acupuncture 1/22 (4%). None had received irreversible treatment, intramuscular injections with botulinum toxin, cognitive therapy or general relaxation exercises. Twelve patients (55%) had received treatment or performed exercises the last six months. Trauma to the face before baseline examination was reported by 3/22 (14 %) and in the time between baseline and follow-up examination by one participant.

Questionnaire

In the follow-up assessment, 12 patients (55%) were found to have low or no limitation of the jaw function (JFLS activities <5). Mean JFLS (SD) was 0.7 (0.87). The frequencies of the pain severity grades (GCPS) were grade 0: 5/22 (23%), I: 14/22 (64%), II: 2/22 (9%), III: 0/22 (0%), and IV: 1/22 (4%).

No patients reported symptoms from other joints.

Imaging findings

The 22 patients with erosive TMJ findings (17 unilateral and 5 bilateral) were reduced to 9 (7 unilateral and 2 bilateral) at follow-up. Our data revealed a statistically significant reduction in the proportion of patients with erosive findings at follow-up, 59.1%, 95% CI [36.4 to 79.3].

In the 44 joints, there was a statistically significant reduction in joints with destruction between baseline and follow-up (right TMJ p <0.034, left TMJ p < 0.002). The longitudinal changes of the condylar erosive findings are shown in Table 1. Improvement of the erosive TMJ findings was a dominant feature and was found in 9/12 (75%) of the right and in 14/15 (93%) of the left TMJs. Repair of the erosive findings, that is, development of an intact cortical outline, was observed in 6/12 (50%) on the right side and in 9/15 (60%) of the left side (Figure 2). Worsening of the erosive findings or joints with new erosive findings in the contralateral joint was rare (Figure 3).

In the 44 TMJs, no significant change was found in the additional hard tissue findings between baseline and follow-up, except for osteophytes that increased significantly (right TMJ p <0.046, left TMJ p < 0.003). At follow-up, the osteophytes were mostly found in joints that were erosive at both examinations (right TMJ: 3/5, left TMJ: 4/6). They were also found in erosive joints that repaired (right TMJ: 0/6, left TMJ: 3/9) and in contralateral joints that were non-erosive at baseline (right TMJ: 1/12, left TMJ: 3/15) (Figure 4a, 4b). Of the joints with osteophytes at follow-up about half of them (right 3/4, left 6/10) showed beaking at baseline (Figure 5). The baseline beaking was stable or had disappeared in the other joints. The most common hard tissue findings at baseline and follow-up in the 27 TMJs that were erosive at baseline are shown in Table 2.

The disc position in relation to the bone erosive findings at baseline is shown in Table 3. Of the 35 joints evaluated with MRI, disc displacement was found in 14/17 right TMJs and 16/18 left TMJs. The majority had DDwoR and all of those showed a completely displaced disc. With one exception, severe disc displacement was found in all TMJs with DDwoR (Figure 4c, 4d). Erosive findings at baseline were mainly found in joints with DDwoR (right TMJ: 9/11, left TMJ: 12/12). In TMJs with a normal disc position, erosive findings were not observed. At follow-up, about half of the joints with erosive findings and DDwoR at baseline had repaired (right TMJ: 4/9, left TMJ: 7/12).

DISCUSSION

The present study documents the unique regeneration potential of the mandibular condyle. Improvement of the osseous status of the TMJ was a dominant feature and worsening of the erosive findings was uncommon, although it should be emphasized that the patient series is

small. At follow-up, repair, that is development of an intact cortical outline, was found in over half of the joints with erosive findings at baseline. Remarkably, the majority of the repaired joints showed no other bone abnormalities. The regeneration capacity of the mandibular condyle is well known particularly in young individuals, for instance after fracture. Very few studies have investigated or documented this phenomenon in adolescents with TMJ- related symptoms.

To our best knowledge, there are only two radiological follow-up studies on erosive TMJ abnormalities (20, 21). A case report documented three patients with erosive findings that developed into articular surface flattening with an intact cortical outline (20). Condylar repair of erosive findings was also shown in a recent study of adolescents followed for 6-12 months (21).

In the present study condylar surface flattening and subcortical sclerosis had similar frequencies at both examinations. In contrast, the frequency of osteophytes increased significantly, and they were mostly found in joints with erosive findings at follow-up. These findings are in accordance with a review of joints in general, stating that osteophyte formation is strongly associated with cartilage damage. However, the review also states that osteophytes may occur without such damage (22). In the present study osteophytes also developed in joints without baseline erosions. The review brings up the discussion whether osteophytes are a pathological phenomenon or a functional adaptation. The authors conclude that osteophytosis is a common feature of OA and can result in clinically relevant symptoms. On the other hand, they also state that osteophytes can be present without negative effects or even have positive effects by increasing the joint surface (22). In line with these statements, the osteophyte formation in the present sample could also be considered a functional remodeling.

The change of the condylar shape seems to have started at baseline when the majority of those joints showed condylar beaking. It should be emphasized though, that it could be challenging to distinguish between a small osteophyte and beaking.

The majority of patients had used masticatory muscle exercises and occlusal splint appliances or had received other non-surgical treatment. Due to the small sample size and the fact that the information about received treatment was collected retrospectively, we did not test for correlation between differences in treatment and TMJ findings. The impact of treatment should be investigated in a prospective manner, in future studies on larger series of patients.

Even when assessing the bone with the most superior methods (CT/CBCT), interpretation of the articular surface was challenging. A recent review underlined that the diagnosis of adult OA should be based on evident changes and not on subtle change that may mimic anatomic variation (12). In children and adolescents, the differentiation between small anatomic variations and pathological signs is even more challenging (10). In the present study we used the criteria defined by Ahmad et al (9), but could not apply the criteria for surface erosion "loss of continuity of articular cortex ", since the cortical layer of the condyle starts to develop at the age 12-14, and is not complete until the age 21-22 (8). Thus, in healthy, growing individuals, the cortical layer is missing or is only partially formed, and surface discontinuities are common. We therefore modified the surface or bone erosion criteria to distinguish between 1) "surface destruction", a surface defect which involved the underlying bone and 2) "surface irregularity", a minor surface defect not involving the underlying bone. The majority of joints had "surface destruction", an undisputable sign of abnormality.

Of the few available cross-sectional CBCT studies of symptomatic adolescents and young individuals with OA-like TMJ disease, the majority report bone erosive signs as the main

TMJ finding (1, 2, 23). In contrast, proliferative signs (sclerosis and osteophytes) and surface flattening are reported as the main findings in asymptomatic individuals or non-patients (1, 2, 24). The dynamic nature of the TMJ findings as revealed in the present study may explain the apparent discrepancy of the observations in the above-mentioned studies. Our results showed erosive findings at baseline and more proliferative findings at follow-up, indicating that the observed signs will be highly influenced by the stage of development and the adaptation of the joint.

The relationship between DDwoR and OA in the TMJ is frequently discussed, and an association has been reported in adolescents (23, 25). The results from the present study are in line with this finding. Erosive findings were found in the majority of the joints with DDwoR, compared to only a few joints with DDwR and no joints with a normal disc position. Whether OA is a consequence of disc displacement, or vice versa, is still debated, and our study cannot contribute to answer this question. What is clear is that almost in all joints with DDwoR the disc was completely displaced, that is displaced in all sections through the joint, definitely a pathological condition (12, 19). Moreover, in those joints the disc displacement was severe, that is the disc was located with its intermediate zone or posterior band caudally to the articular eminence in all sections at closed mouth.

To the best of our knowledge, the present study is the first one to demonstrate improvement of erosive findings in such a large proportion of joints with a non-reducing disc. Eleven of the 21 joints with erosions and DDwoR (4 right and 7 left) had repaired and developed an intact cortical outline at follow-up. This was an unexpected observation. Traditionally, non-reducing disc displacement is thought of as a severe form of internal derangement and frequently, at least by many, considered to be related to the development of osteoarthritis.

Most terms used to describe the OA-like abnormalities in children and adolescents are similar to those applied for adults: degenerative joint changes (23), condylar bony changes (3), condylar degeneration (26), osteoarthrosis (2), osteoarthritic changes (1), and OA (20, 24). A "juvenile" term, juvenile OA, has been introduced (10). Another term, arthrosis deformans juvenilis, was introduced in 1966 and was associated with facial growth disturbances (27). Later, several terms have been proposed: condylar resorption, idiopathic condylar resorption, progressive condylar resorption, adolescent internal condylar resorption, condylysis, etc. when erosive disease is related to facial deformities (4).

Erosive TMJ disease in adolescents usually is considered a form of degenerative joint disease and the opinions on whether or not it is inflammatory are divergent (5). Recently, a study comparing this disease with juvenile idiopathic arthritis (JIA) convincingly demonstrated that both diseases were inflammatory (6). This is in line with adult OA, being regarded as a low-inflammatory disease both in the TMJ and in other joints (28-30). JIA is therefore an important differential diagnosis. It frequently involves the TMJ unilaterally in early phase but usually progresses into bilateral involvement (31). Bone abnormalities can be similar in both disease groups. However, frequently the disc is normally located in JIA (32), in contrast to erosive TMJ disease in which the disc is usually displaced. When the disc occasionally is displaced in JIA (33), it may be difficult or impossible to radiologically distinguish JIA from erosive TMJ disease. The imaging signs that may differ between the diseases are a more pronounced inflammation and a more flattened fossa/eminence in JIA (6). In the present study, none of the patients reported other joints with inflammatory signs (pain/swelling/reduced function) in the follow-up interview. Serologic tests for arthritis are often negative in JIA patients. When there is uncertainty about the diagnosis, the patient should be referred to a pediatric rheumatologist.

Idiopathic condylar resorption (ICR) also needs to be further discussed. Whether this condition is a separate disease entity, or an aggressive form erosive TMJ disease (4), is unclear. ICR is usually bilateral and progressive, resulting in facial growth disturbances and malocclusion (5). In our study, 3 out of 4 patients had unilateral affection without clinically evident facial growth disturbances, and frequently the erosive findings improved. However, bilateral erosive findings did occur which could represent an early phase of ICR, before facial deformities are evident. However, also these patients improved. It seems to be impossible to differentiate between ICR and erosive TMJ disease by TMJ imaging findings alone, and they may show similar progression (5). Occasionally, ICR is unilateral. One 12-year old patient in the present study showed unilateral progression of the erosive findings during a 1.5- year follow-up period. This might be such a case.

The present study is focusing on the imaging features of OA-like TMJ disease in young patients, but self-experienced symptoms were also recorded. Self-experienced pain seemed quite low for most of the patients in the follow-up assessment. The vast majority (86%), had low-intensity pain without disability (GCPS grade 1) or no pain at all (GCPS grade 0). It was, however, challenging to evaluate the results of the jaw functional limitation assessment. Since no cut-offs yet have been provided for the interpretation of JFLS (17), we considered patients who rated any of the JFLS questions with a score 5 or higher to have significant limitation while the remaining patients were classified as having low or no limitation (14). Significant limitation was found in as many as 10 (45%), but our mean JFLS (0.7) seemed quite low, especially compared to a Swedish study of adolescent females (16-19 years) with self-reported symptoms and mean JFLS of 5.8 (34). This may indicate that the participants had a significant limitation in a limited number of situations. The GCPS and JFLS were not

assessed at baseline and a comparison with the follow-up assessment could not be made. However, we speculate that the symptoms had improved as all patients had TMJ-related pain and most of them also had dysfunction when referred to us at baseline. Although pain and other symptoms have been associated with bone erosions in adolescents(1), it is known that symptoms may fluctuate and frequently do not correlate with imaging findings (12). In a short-term follow-up of adults (mean age 26.9 years) with TMJ OA, pain reduction was reported irrespectively of the imaging findings (35).

Study limitations need mentioning. Dropouts are common in longitudinal studies and something we have experienced. Of the 42 invited participants, 12 declined or did not show up for assessments and six were excluded. The small sample size limited the statistical analyses and precision of our estimates. Whether the non-participants had more or less severe disease (or symptoms) is unknown, and our findings can therefore only be generalized to a subgroup of adolescents with erosive TMJ findings who experience (and seek help for) TMJ-related pain. Further, as participation was voluntary, we cannot exclude selection bias.

Small sample sizes often evoke skepticism about whether the collected data can be subjected to a statistical test, as studies have limited statistical power and thus can often suffer type II error. Our study was sufficiently powered for the main outcome. When conducted the power calculation, we anticipated the proportion of patients experiencing reduction of erosive findings to be at least 50%. Keeping the customary significance level alpha of 5%, we would need 25 individuals to achieve a level of precision of 10%. To achieve a lower level of precision of +- 15%, we would need 12 patients. Thus with 22 included individuals we consider our study sufficiently powered.

Other weaknesses of this study are that the baseline imaging techniques were not standardized, and that the osseous criteria are not validated for this age group. Future studies are therefore needed. To enhance the validity of the CBCT interpretation, we used two experienced radiologists to render consensus diagnoses, rather than depending on a single radiologist. However, the longitudinal changes of erosive findings from baseline to follow-up were assessed using a side by side comparison, which is a method susceptible to detection bias. Regarding the follow-up questionnaires, they have not been validated in individuals below 18 years of age. However, they are both used in studies in young populations and are considered appropriate and adapted for Scandinavian culture (34).

Our results should be confirmed with larger studies using validated criteria and symptom registration both at baseline and at follow-up. Future studies may also investigate whether the degree of condylar development, age and the length of follow-up time, as well as the type of treatment/intervention, have an impact on the outcome of bone changes.

CONCLUSION

Improvement of the bony TMJ erosions was the dominant feature in this series of adolescents with TMJ-related symptoms. Half of the joints with destruction of the condylar surface involving the underlying bone repaired, the majority without other radiological abnormalities. Osteophytes were common at follow-up, and most of them were found in joints with erosive findings. At follow-up, more than half of the patients reported low or no limitation of the jaw function. The majority of patients assessed their symptom severity as low.

AUTHORS CONTRIBUTION

Study design: AKA, LZA, MCS, TAL.

Collection and assembly of data: AKA, LZA, TAL.

Analyses and interpretation of data: AKA, LZA, MCS, TAL.

Drafting the article: AKA, LZA, MCS, TAL.

Revising the article critically and final approval: AKA, LZA, MCS, TAL.

Statistical analyses: AKA, MCS.

Obtaining of funding: -

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest in regard to this work.

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Table 1. Condylar changes of erosive CT/CBCT findings from baseline to follow-up in 22 adolescents/young adults (n=44 TMJs)

	Right TMJs n=22 joints		Left TMJs n=22 joints	
Baseline**:**	Erosive n=12	Non-erosive n=10	Erosive n=15	Non-erosive n=7
Follow-up: Improvement	9 [1]	0	14 [2]	0
No change	2	9	1	6
Worsening	1	1	0	1

[1] Six developed an intact cortical outline
[2] Nine developed an intact cortical outline

CT, computed tomography
CBCT, cone beam computed tomography
TMJ, temporomandibular joint

Table 2. Condylar findings at baseline and at follow-up in 22 adolescents/young adults (n= 27 TMJs)

CT/ CBCT Findings [1,2]		Right TMJ n =12		Left TMJ n =15	
		Baseline	Follow-up	Baseline	Follow-up
Erosive findings	Surface destruction	11	3	10	1
	Surface irregularity	1	2	5	5
Articular surface flattening		9	8	13	12
Subcortical sclerosis		4	6	5	2
Beaking		4	1	5	1
Osteophyte		0	3	1	7

[1] Defined according to Ahmad et al (9) with author-based modifications

[2] At baseline and follow-up, few joints were registered with condyle subcortical cyst, hypoplasia and deviation in form, or fossa eminence articular surface flattening and subcortical sclerosis. No joints were registered with loose calcified body, bony ankylosis, generalized condylar sclerosis, condylar hypoplasia, fossa/ eminence- irregularity or destruction

TMJ, temporomandibular joint
CT, computed tomography
CBCT, cone beam computed tomography

Table 3. Disc position in relation to erosive findings at baseline in 18 adolescents/young adults (n=35 TMJs)

MRI findings of disc position at baseline[1]	Right TMJ n= 17[2]		Left TMJ n= 18	
	All	Erosive	All	Erosive
Normal	3	0	2	0
Anterior displacement with reduction	3	2	4	0
Anterior displacement without reduction	11	9	12	12
Total joints	17	11	18	12

[1]Defined according to the diagnostic criteria by Drace and Enzmann (18)

[2] One joint could not be evaluated due to suboptimal image quality

TMJ, temporomandibular joint
MRI, magnetic resonance imaging

Figure 1

Flow-chart showing inclusion and detailing the reason for decline or exclusion in a CBCT follow-up of symptomatic adolescents with erosive TMJ findings

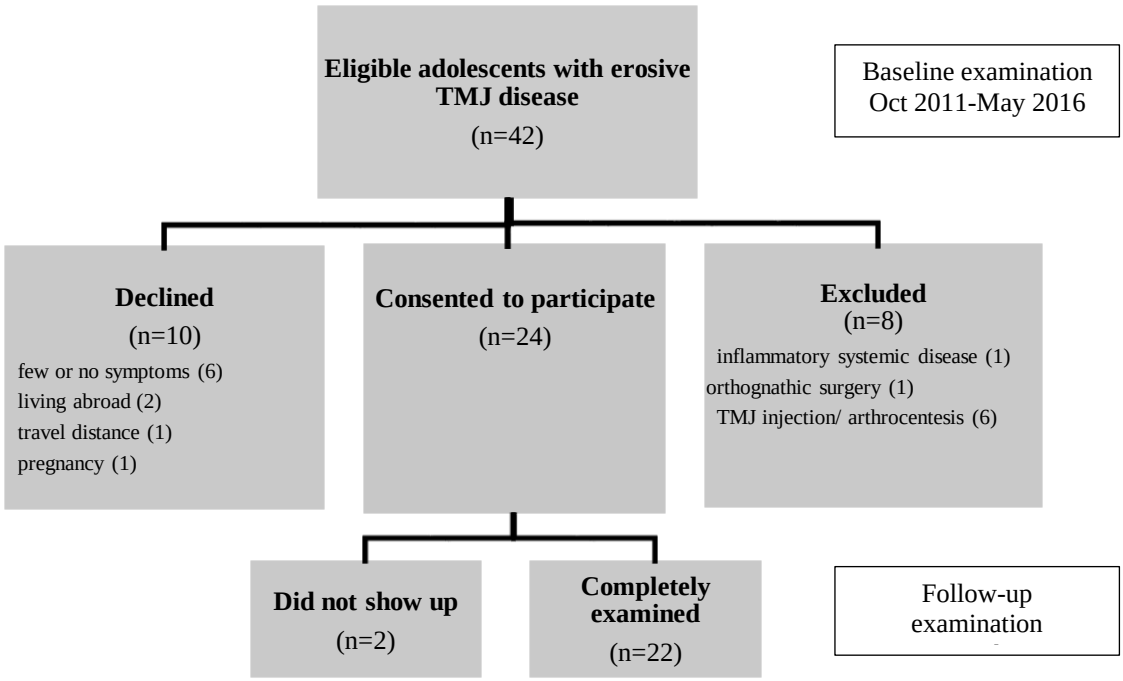

Figure 2

Three females, 13 (a), 15 (c), and 18 (e) yrs at baseline, with 4.4 (b), 6.4 (d), and 4.8 (f) yrs follow-up. Surface destruction repaired with development of an intact cortical outline, more evident in the two older patients (c,d and e, f) than in the youngest one (a, b). The condyle has normalized in shape (a, b), showed some articular surface flattening with similar shape at baseline and at follow-up (c, d), and showed more severe surface flattening of condyle (and fossa/eminence) (e, f)

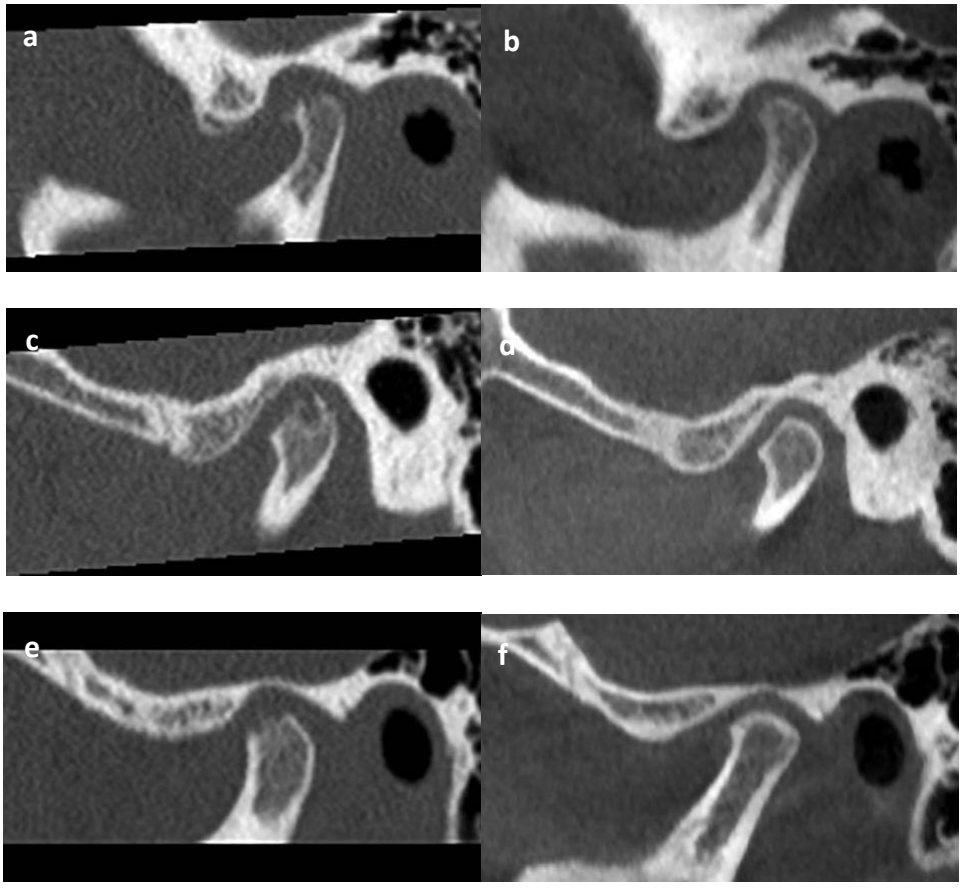

Figure 3

Female, 11 yrs at baseline (a) with 1.3 yr follow-up (b). Condylar destruction (a) shows progression (b)

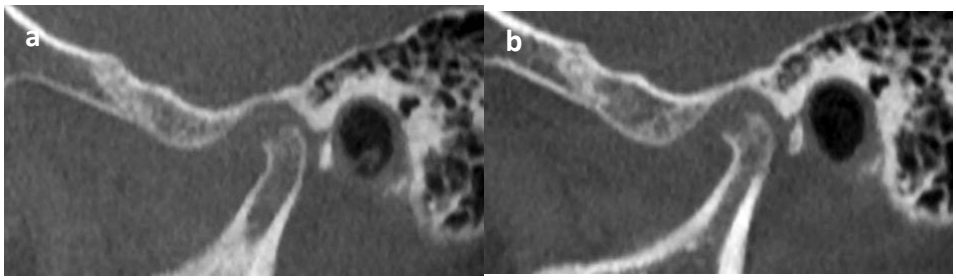

Figure 4

Female, 18 yrs at baseline (a) with 2.7 yr follow-up (b). Surface destruction (a) is replaced by irregular cortical outline and osteophyte (b). Closed mouth MRI at baseline shows severe disc displacement; disc displaced with its intermediate zone and posterior band caudally to the eminence (c) and non-reducing disc on open mouth image (d)

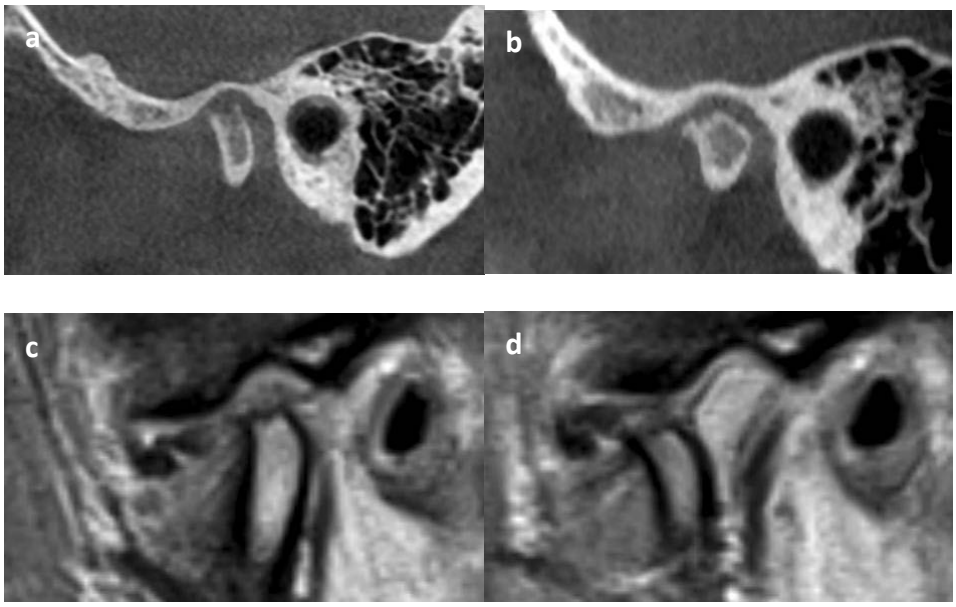

Figure 5

Female, 16 yrs at baseline (a) with 3.5 yr follow-up (b). Condylar beaking (a) has developed into an osteophyte (b).