Biological markers and cognitive function in painful temporomandibular disorder

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Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The scientific research comprising this thesis was performed at the University of Bergen (UoB), Norway, and Haukeland University Hospital (HUH) in Bergen, and was part of a multidisciplinary evaluation programme for TMD patients, initiated and partly financed by The Norwegian Directorate of Health.

The evaluation of TMD patients in Study Ia and Ib was performed at the Department of Oral and Maxillofacial Surgery and the Pain Clinic at HUH in Bergen, Norway. The examination of the control group in study Ia was performed at the Department of Clinical Dentistry, UiB. Ersilia Bifulco, from The Department of Clinical Science (DCS) at the UoB, performed the LC-MS/MS analysis at the Core Facility for Metabolomics. Professor Steinar Hustad from DCS gave support and feedback on the results of the analyses. The blood sampling of both patients and controls in Study Ia was performed at HUH and analyzed at the Laboratory for Clinical Biochemistry. The neurocognitive testing of TMD patients and healthy controls in Study II was performed at the Neuropsychological Clinic at the Faculty of Psychology, University of Bergen.

The supervisor group which bridges the Medical and Psychological faculties at University of Bergen (UoB) and the HUH consisted of Professor Annika Rosén as the main supervisor, and co-supervisors Professor Åsa Hammar, Professor Anders Johansson, and Professor Arne Tjølsen.

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Abbreviations

5HT	Serotonin
CCL	Chronic closed lock
CNS	Central nerve system
CSQ	Coping Strategies Questionnaire
CWIT	Color Word Interference Test
DC/TMD	Clinical Diagnostic Criteria for TMD
EF	Executive function
fMRI	functional magnetic resonance imaging
Gr	Subgroup in Paper III
HADS	Hospital Anxiety Depression Scale
HPA axis	Hypothalamic-pituitary-adrenal axis
HUH	Haukeland University Hospital, Bergen, Norway
IASP	The International Association for the Study of Pain
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
ICD-10	International Classification of Diseases, Tenth Revision
LC	Locus coeruleus
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
MRI	Magnetic resonance imaging
NGF	Nerve growth factor

OPG	Orthopantomogram
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment study
PC	Painful clicking
PTH	Para-thyroid hormone
pTMD	painful temporomandibular disorders
QoL	Quality of life
RDC/TMD	Research Diagnostic Criteria for TMD
S	Subtest
TMD	Temporomandibular disorders
TMJ	Temporomandibular joint
TMJD	Temporomandibular joint disorder
TNF-α	Tumor necrosis factor alpha
TRPV1	Transient receptor potential, subfamily V, member 1
UoB	University of Bergen, Norway

Abstract

Background and aims: Painful temporomandibular disorders (pTMD) are characterized by pain and dysfunction in the masticatory apparatus and the temporomandibular joint (TMJ). The overall aim of this thesis was to characterize a patient group with refractory pTMD that was referred to an interdisciplinary examination programme, to improve investigation and develop preventive and early treatments. Specific aims were to investigate pTMD patients': 1) stress and HPA-axis activity, 2) biomarkers in blood samples, 3) risk factors, and 4) neurocognitive functioning.

Methods: The present study was part of a national interdisciplinary evaluation programme for pTMD patients at Haukeland University Hospital (HUH) in Bergen, Norway initiated by the Norwegian Health Directorate. In total, 129 pTMD patients were referred from their general practitioners and examined during the years 2013-2017.

Study I consisted of the first 60 pTMD patients from the interdisciplinary programme at HUH, and 60 healthy gender- and age-matched controls. The first part of the study was a controlled cross-sectional study, where saliva samples were taken in the morning and analyzed for cortisol and cortisone with liquid chromatography–tandem mass spectrometry (LC-MS/MS). Psychosocial stress was measured by means of questionnaires, including the Hospital Anxiety and Depression Scale (HADS) and a 2-item version of the Coping Strategies Questionnaire (CSQ). After exclusion of patients due to different causes, data from 44 TMD patients and their 44 respective controls were included in *Paper I*. In addition, blood samples from all 60 pTMD patients and 60 controls from *Study I* were analyzed, retrieving 19 different analyses of essential proteins, hormones, electrolytes, and vitamins (*Paper II*). The second part of *Study I* was a longitudinal study, with a three-year follow-up of the 60 pTMD patients (*Paper III*). A questionnaire that covered medical history, function, pain, lifestyle factors, TMD status, and questions about the follow-up from their general medical practitioner (GMP), was sent to the patients approximately three years after the investigation. Questionnaires that assess function (Mandibular Functional Index Questionnaire, MFIQ and Roland

Morrison Scale, RMS), pain intensity (General Pain Intensity Questionnaire, GPI) and psychosocial stress HADS and CSQ were incorporated.

Study II was a controlled cross-sectional study, where the population was extended to include all 129 pTMD patients. A new matched control group was recruited. Neurocognitive function was tested with a four-item Color Word Interference Test (CWIT). An IQ test (Wechsler Abbreviated Scale of Intelligence (WASI) two-item) was performed to confirm that the pTMD group was comparable to the control group. Included questionnaires were the Rumination Response Scale (RRS), Rumination Reflection Questionnaire (RRQ), Oral Health Impact Profile- TMD (OHIP-TMD), General Pain Intensity (GPI), Montgomery Åsberg Depression Rating Scale (MADRS-S), and the Perceived Deficits Questionnaire (PDQ-5) (*Paper IV*).

Results: The 60 first pTMD patients *(Paper I, II & III, Study I)* included 51 women and nine men. Mean age was 45 years (range 20-69), and mean pain duration was 11 years (range 1-40) in the pTMD group. The TMD diagnoses in the pTMD group were myalgia (n = 22), arthralgia (n = 1), disc derangement (n = 2), and combinations (n = 35). In *Paper I,* cortisol and cortisone concentrations in saliva were significantly higher in the pTMD group compared to the control group ($p=0.01$ and $p=0.04$, respectively). Psychosocial stress measured by HADS and CSQ was also significantly higher ($p<0.001$) in the pTMD patient group. In *Paper II,* we observed that TMD patients had significantly higher concentrations of hemoglobin ($p=0.036$), cobalamin ($p=0.023$), albumin ($p=0.005$), parathyroid hormone (PTH) ($p=0.038$), and vitamin D ($p=0.005$), but significantly lower values of creatinine ($p=0.006$) and potassium ($p=0.011$) in the blood samples compared to the controls. However, most of the pTMD patients and the controls had values within normal biological range. In *Paper III*, 39 out of 60 TMD patients completed the questionnaires in the three-year follow-up study. Improvements of the TMD symptoms were reported in 10 patients (26%), unchanged in 16 patients (41%), and worsened in 13 patients (33%). Significant improvements of symptoms were noted in jaw function (MFIQ), pain intensity at maximum, suffering from pain, and pain catastrophizing. A high pain intensity at baseline was a significant risk factor *(OR=5.*79,

95% CI: 1.34, 24.96) to report worsening of TMD symptoms at follow-up. In *Paper IV*, 22 (20 women and two men) of the 129 patients with pTMD from *Study II* were included and tested. There were no significant differences in age, sex distribution, IQ, or educational level between the pTMD group and the group of 19 controls. Mean pain duration in the pTMD group was 21 years (range 7-42). The pTMD patients reported a high pain intensity ($p<0.001$), duration of pain, rumination (RRS/ RRQ, $p = 0.003$ / $p = 0.021$), and depression (MADRS-S, $p < 0.001$) compared to the control group. Self-perceived neurocognitive function (PDQ-5, $p < 0.001$) and quality of life related to oral health (OHIP-TMD, $p < 0.001$) were significantly lower in the patient group. No significant differences were observed from the neurocognitive testing (CWIT) between the pTMD patients and the control group.

Conclusions: The pTMD patients in our study suffered from high levels of psychosocial stress, including self-perceived cognitive deficits, anxiety, depression, rumination, pain-related catastrophizing, and low QoL related to oral health. All the above factors might be important characteristics of pTMD. These factors may make it more difficult to master chronic pain and common everyday tasks, suggesting that they could be targeted in treatment and interventions. However, the neurocognitive performance in *Paper IV* was equivalent to the control group. Higher pain intensity in patients with pTMD was significantly associated with poorer recovery, indicating that patients with high pain intensity might be at risk of refractory TMD. The pTMD patients had significantly higher concentrations of salivary cortisol and reported higher psychosocial stress compared to a healthy control group, possibly indicating an upregulated HPA axis. We were unable to associate any severe systemic diseases, malnutrition, or systemic inflammation with pTMD, and therefore we would not recommend blood samples for screening of TMD patients.

Abstrakt

Bakgrunn og mål: Smertefull temporomandibulær lidelse (pTMD) er preget av smerte og dysfunksjon i tyggeapparatet og kjeveleddet. Det overordnede målet med denne avhandlingen var å karakterisere en pasientgruppe med residiverende pTMD, for å forbedre utredning og utvikle forebyggende og tidlig behandling. Spesifikke mål var å undersøke pTMD-pasienters: 1) stress og HPA-akseaktivitet, 2) biomarkører i blodprøver, 3) risikofaktorer og 4) nevrokognitiv funksjon.

Metoder: Denne studien var en del av et nasjonalt tverrfaglig utredningsprogram for pTMD-pasienter ved Haukeland Universitetssykehus (HUH) i Bergen, på oppdrag av Helsedirektoratet. Totalt ble 129 pTMD-pasienter henvist fra sin fastlege og undersøkt i løpet av årene 2013-2017.

Studie I besto av de første 60 pTMD-pasientene fra det tverrfaglige programmet ved HUH, og 60 friske kontroller med samsvarende kjønn og alder. Første del av studien var en kontrollert tverrsnitts-studie, hvor spyttprøver ble tatt om morgenen og analysert for kortisol og kortison med væskekromatografi - tandem massespektrometri (LC-MS/MS). Psykososialt stress ble målt ved hjelp av spørreskjemaer, inkludert Hospital Anxiety and Depression-skalaen (HADS) og en 2-spørsmåls versjon av Coping Strategies Questionnaire (CSQ). Etter ekskludering av pasienter på grunn av ulike årsaker, ble data fra 44 TMD-pasienter og deres 44 respektive kontroller inkludert i *Artikkel I*. I tillegg ble blodprøver fra alle 60 pTMD pasienter og 60 kontroller fra *Studie I*, analysert for å hente 19 forskjellige analyser av essensielle proteiner, hormoner, elektrolytter og vitaminer (*Artikkel II*). Den andre delen av *Studie I* var en longitudinell studie, med en treårig oppfølging av de 60 pTMD-pasientene (*Artikkel III*). Et spørreskjema som dekket sykehistorie, funksjon, smerte, livsstilsfaktorer, TMD-status og spørsmål om oppfølging fra deres fastlege, ble sendt til pasientene ca. tre år etter den tverrfaglige utredningen. Spørreskjemaer som vurderer funksjon (Mandibular Functional Index Questionnaire, MFIQ og Roland Morrison Scale, RMS), smerteintensitet (General Pain Intensity questionnaire, GPI) og psykososialt stress HADS og CSQ ble inkorporert i studien.

Studie II var en kontrollert tverrsnitts-studie, hvor populasjonen ble utvidet til å omfatte alle 129 pTMD-pasienter. En ny matchet kontrollgruppe ble rekruttert. Nevrokognitiv funksjon ble testet med en 4-elements Color Word Interference Test (CWIT). En IQ-test (Wechsler Abbreviated Scale of Intelligence (WASI) 2-test versjon) ble utført for å bekrefte at pTMD-gruppen var sammenlignbar med kontrollgruppen. Inkluderte spørreskjemaer var Rumination Response Scale (RRS), Rumination Reflection Questionnaire (RRQ), Oral Health Impact Profile-TMD (OHIP-TMD), General Pain Intensity (GPI), Montgomery Åsberg Depression Rating Scale (MADRS-S) og Perceived Deficits Questionnaire (PDQ-5) (*Artikkel IV*).

Resultater: Den første gruppen med 60 pTMD-pasienter (*Artikkel I, II & III*, *Studie* I) besto av 51 kvinner og 9 menn. Gjennomsnittlig alder var 45 år (fra 20 til 69 år), og gjennomsnittlig smertevarighet var 11 år (fra 1 til 40 år) i pTMD-gruppen. TMD-diagnosene i pTMD-gruppen var myalgi (n = 22), artralgi (n = 1), diskdisplassering (n = 2) og kombinasjoner av disse (n = 35). I *Artikkel I* var kortisol- og kortisonkonsentrasjoner i spytt signifikant høyere i pTMD-gruppen sammenlignet med kontrollgruppen (henholdsvis p=0,01 og p=0,04). Psykososialt stress målt ved hjelp av HADS og CSQ var også signifikant høyere (p<0,001) i pTMD-gruppen. I *Artikkel II* observerte vi at TMD-pasienter hadde signifikant høyere konsentrasjoner av hemoglobin (p=0,036), kobalamin (p=0,023), albumin (p=0,005), parathyroidhormon (PTH) (p=0,038), vitamin D (p) =0,005) og signifikant lavere verdier av kreatinin (p=0,006) og kalium (p=0,011) i blodet sammenlignet med kontrollene. Imidlertid hadde de fleste pTMD-pasientene og kontrollene verdier innenfor normalt biologisk område. I *Artikkel III* fullførte 39 av 60 TMD-pasienter spørreskjemaene i den treårige oppfølgingsstudien. Forbedringer av TMD-symptomene ble rapportert hos 10 pasienter (26 %), uendret hos 16 pasienter (41 %) og forverret hos 13 pasienter (33 %). Signifikante forbedringer av symptomene ble rapportert av pasientene i kjevefunksjon (MFIQ), smerteintensitet på det verste, plagsomhet som følge av smerte, og smerterelatert katastrofetenkning. Høy smerteintensitet ved første målepunkt var en signifikant risikofaktor (OR=5,79, 95 % KI: 1,34, 24,96) for å rapportere forverring av TMD-symptomer ved oppfølging. I *Artikkel IV* ble 22 (20 kvinner og 2 menn) av de 129 pasientene med pTMD fra *Studie II* inkludert og

testet. Det var ingen signifikante forskjeller i alder, kjønnsfordeling, IQ eller utdanningsnivå mellom pTMD-gruppen og gruppen med de 19 kontrollene. Gjennomsnittlig smertevarighet i pTMD-gruppen var 21 år (fra 7 til 42 år). pTMD-pasientene rapporterte høy smerteintensitet ($p<0,001$), smertevarighet, ruminering/ grubling (RRS/RRQ, $p = 0,003$ / $p = 0,021$) og depresjon (MADRS-S, $p < 0,001$) sammenlignet med kontrollgruppen. Selvopplevd nevrokognitiv funksjon (PDQ-5, $p < 0,001$) og livskvalitet relatert til oral helse (OHIP-TMD, $p < 0,001$), var signifikant lavere i pasientgruppen. Ingen signifikante forskjeller ble observert fra nevrokognitiv testing (CWIT) mellom pTMD-pasientene og kontrollgruppen.

Konklusjon: pTMD-pasientene i vår studie led av høye nivåer av psykososialt stress, inkludert selvopplevde kognitive vansker, angst, depresjon, grubling, smerterelatert katastrofetenkning og lav livskvalitet relatert til oral helse. Alle de ovennevnte faktorene kan være viktige karakteristika ved pTMD. Disse faktorene kan gjøre det vanskeligere å mestre kroniske smerter og vanlige hverdagsoppgaver, noe som tyder på at behandling og intervensjoner bør rettes mot disse. Imidlertid var den testede nevrokognitive funksjonen ekvivalent med kontrollgruppen. Høyere smerteintensitet hos pasienter med pTMD var signifikant assosiert med forverring av symptomene, noe som indikerer at pasienter med høy smerteintensitet kan ha risiko for refraktær TMD. pTMD-pasientene hadde signifikant høyere konsentrasjon av kortisol i spyttet og rapporterte høyere psykososialt stress fra spørreskjemaer, sammenlignet med en frisk kontrollgruppe, noe som muligens indikerer en oppregulert HPA-akse. Vi var ikke i stand til å assosiere noen alvorlig systemisk sykdom, underernæring eller systemisk betennelse med pTMD-pasientene, og derfor vil vi ikke anbefale blodprøver for screening av TMD-pasienter.

List of Publications

Staniszewski K, Lygre H, Bifulco E, Kvinnsland S, Helgeland E, Willassen L, Berge T, Rosen A (2018): 'Temporomandibular Disorders Related to Stress and HPA axis Regulation.' *Pain Res Manag. 2018:7020751. doi: 10.1155/2018/7020751.*

Staniszewski K, Lygre H, Berge T, Rosen A (2019): 'Serum Analysis in Patients with Temporomandibular Disorders: A Controlled Cross-Sectional Study in Norway.' *Pain Res Manag. 2019:1360725. doi: 10.1155/2019/1360725.*

Staniszewski K, Willassen L, Berge T, Johansson A, Schjødt B, Rosen A (2022): 'High Pain Intensity is a Risk Factor of Non-Resolving TMD: A Three-Year Follow-Up of a Patient Group in a Norwegian Interdisciplinary Evaluation Program.' *J Pain Res. 2022:2;15:1283-1296. doi: 10.2147/JPR.S341861.*

Staniszewski K, Ronold EH, Hammar Å, Rosén A (2023): 'Neurocognitive functioning in patients with painful temporomandibular disorders.' Submitted *J Pain Res.*

Contents

1. Introduction

Temporomandibular disorders (TMD) are characterized by pain and dysfunction in the temporomandibular joint (TMJ) and the masticatory muscles (Slade et al. 2016) (Scrivani et al. 2008).The prevalence of TMD has been estimated at 3-15% in the general population (Helsedirektoratet 2016; Johansson et al. 2003), occurring predominantly in women (Hoffmann et al. 2011). Most cases of TMD are mild (Schiffman et al. 1990; Velly et al. 2022); however, some patients develop chronic TMD pain and disability (Rudy et al. 1995; Velly et al. 2022). TMD has been linked to a states of comorbidity including other painful disorders, depression, frequent trauma, and stress symptoms (Hoffmann et al. 2011; Kotiranta et al. 2019). A significantly higher prevalence of psychosocial factors associated with TMD compared to a healthy population was revealed by the OPPERA study (Fillingim et al. 2011; Slade et al. 2016).

1.1 Historical perspective

Temporomandibular disorders (TMD) have a long historical perspective. In 1934, James B. Costen coined the term "Costen syndrome" when he first described the symptoms TMJ and masticatory muscles (Costen 1934). Costen suggested that malocclusion and anatomical positioning of the mandible caused pain and TMD symptoms. However, his hypothesis of malocclusion as a causality of TMD failed to become evidently proven (Türp and Schindler 2012). In 1992, the first evidence-based diagnostics of TMD was published, named the Research Diagnostic Criteria for TMD (RDC/TMD) (Dworkin and LeResche 1992). A modified version of diagnostic criteria with treatment recommendations has been published in Norway (Helsedirektoratet 2016). The evidenced based explanation of TMD has progressed through the past three decades from pathology- and anatomy of the TMJ to a multifactorial biopsychosocial model, including frequent musculoskeletal pain in addition to psychological disabilities (Ohrbach and Dworkin 2016; Scrivani et al. 2008; Suvinen et al. 2005) .

1.2 Symptoms

TMD is a common term of the syndrome characterized by pain and dysfunction of the masticatory muscles with frequent involvement of the TMJ (Helsedirektoratet 2016). The primary symptoms of TMD are facial pain and dysfunction of the mandible, including limited opening capacity and impaired chewing ability. TMD symptoms may sometimes be accompanied with painful clicking in the TMJ. Other common symptoms include tinnitus, dizziness, ear pain, neck and shoulder pain, headaches, and depression (Scrivani et al. 2008; Suvinen et al. 2005). The TMD symptoms can range from mild to severe in intensity, and in most patients the symptoms relieve without treatment or with conservative treatment only. However, in some cases, TMD can be severe and may lead to chronic pain accompanied by physical, behavioural, psychological, and psychosocial disability in affected patients (Scrivani et al. 2008; Slade et al. 2016). Associated comorbidities which are often observed along with TMD include fibromyalgia, chronic fatigue, degenerative arthritis, irritable bowel syndrome , and depression, in additional to frequent trauma and stress symptoms (Hoffmann et al. 2011; Kotiranta et al. 2019; Slade et al. 2016).

1.3 Prevalence

In Norway, TMD is assumed to have a 3-15% prevalence in the general population (depending on which diagnostic criteria is used), with first occurrence mainly in age 20-45 years (Helsedirektoratet 2016). However, TMD may also occur in children and elderly (Helsedirektoratet 2016). In the population older than middle age, the prevalence of TMD has been estimated to be 2-12% (Isong et al. 2008; Johansson et al. 2003). The prevalence of painful TMD in adolescents diagnosed with RDC/TMD lies probably within 2-7% (LeResche et al. 2007; List et al. 1999; Nilsson 2007; Østensjø et al. 2017).The OPPERA study reported a 4% incidence per year of first onset of TMD (Slade et al. 2016). The risk of first onset of TMD has also been associated with other painful symptoms, including headache and pain in other body parts (Sanders et al. 2013; Slade et

al. 2013). Results from a review showed that approximately 5% of adults have reported experiencing jaw or facial pain within the past three months (Maixner et al. 2016). The prevalence of TMD is at least twice as high in women as men, and women present with an increased severity of the disorder (Bueno et al. 2018; Hoffmann et al. 2011).

1.4 Etiology and Characteristics

The most reasonable explanation of TMD today is as a complex multifactorial biopsychosocial mechanism, including frequent musculoskeletal pain in addition to psychosocial factors (Bair et al. 2016; Fillingim et al. 2018; Ohrbach and Dworkin 2016; Slade et al. 2016). However, whether there exists a specific pathophysiology behind TMD that differs from other musculoskeletal disorders is currently unknown. Results from a community-based cohort study found that risk factors for TMD onset included jaw function, pain sensitivity, sleep quality, and psychosocial factors. The observed risk factors were also reinforced and sustained in individuals whose TMD persisted over several years (Ohrbach et al. 2020).

1.4.1 Psychosocial Factors

Psychosocial factors have been accepted as potential risk factors of TMD (Fillingim et al. 2018; Slade et al. 2016; Willassen et al. 2020). A significantly higher prevalence of psychosocial factors like somatic awareness, distress, catastrophizing, and psychosocial stress in subjects with TMD compared to healthy individuals has also been linked to TMD in a large longitudinal study in the US (the OPPERA study) (Slade et al. 2016) (Fillingim et al. 2011). Multifactorial personal characteristics, in addition to changes in biopsychosocial functioning over time, are thought to be crucial in development and persistence of TMD (Ohrbach et al. 2020). Results from a large longitudinal study showed that catastrophizing and depression were associated with increased pain intensity as well as disability in TMD patients (Velly et al. 2011). Anxiety and depression have also been related to significantly higher pain intensity and disability in patients with general musculoskeletal pain (Bair et al. 2008).

1.4.2 Pain Sensitivity

TMD patients have shown to differ from healthy individuals in elevated pain amplification and pain sensitivity (Slade et al. 2016). Several studies have found associations between the severity of TMD and reduced pressure pain thresholds (PPT), suggesting that altered pain modulation may play a significant role in the development and persistence of painful TMD (Herpich et al. 2018; Stuginski-Barbosa et al. 2015).

1.4.3 Hormones

The mechanisms behind the remarkably higher prevalence and severity of TMD in women is also currently being discussed. Results from the OPPERA study have shown that most pain measurements have a significantly higher pain sensitivity in women compared to men (Ostrom et al. 2017). The conclusions of previous reviews were that the higher prevalence and severity of pain in women might be explained by a multifactorial biopsychosocial mechanism including sex hormones, endogenous opioid function, genetic factors, pain coping, pain-related catastrophizing, and gender roles (Bartley and Fillingim 2013). Animal studies have demonstrated that testosterone may have an antinociceptive effect (Borzan and Fuchs 2006), while estradiol may have a pronociceptive effect on pain sensation (Li et al. 2009) which strengthens the claim of sex steroid involvement in painful conditions.

1.4.4 Other Etiologic Factors

Populations of TMD patients have shown a higher prevalence of physical trauma compared to the general healthy population (Hoffmann et al. 2011). In a small population of TMD patients, previous physical trauma was associated with higher severity of the disorder as well as higher psychosocial disabilities (Kim et al. 2010). TMJ internal derangement, often characterized by painful clicking in the TMJ, may cause mechanic stress and inflammation in the TMJ, and has been associated with TMJ effusion, TMJ pain, and headache (Costa et al. 2008). Results from a hospital-based case-control study also identified autoimmune diseases and inflammatory conditions as a risk factor for the development of TMJ disease (Fredricson et al. 2018). Oral parafunctional habits, including teeth clenching and jaw tensing, may add a repetitive

masticatory muscle tension and contribute to myofascial pain (Fricton 2007). An association between general joint hypermobility and closed chronic lock (CCL) has also been observed (Ögren et al. 2012).

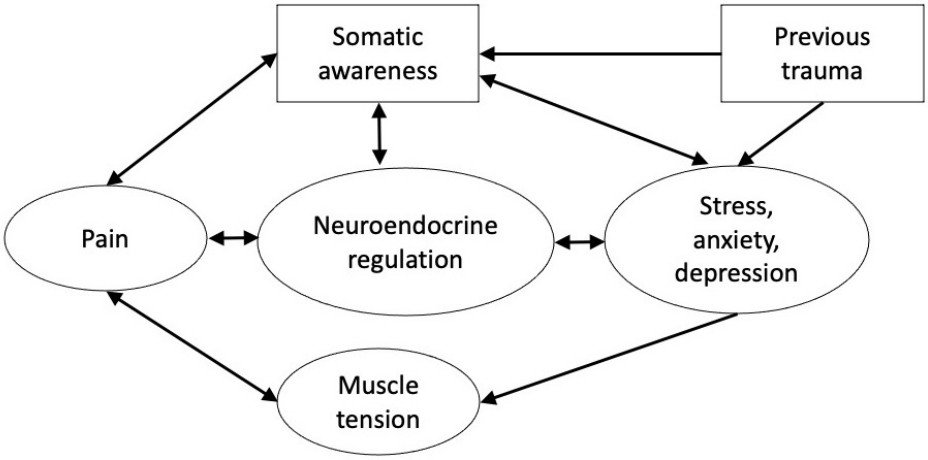

Figure 1; Suggested by the author of the present thesis, the etiology of TMD might be explained by a complex biopsychosocial model where different factors may affect and reinforce each other.

1.5 TMJ Anatomy

1.5.1 TMJ Function

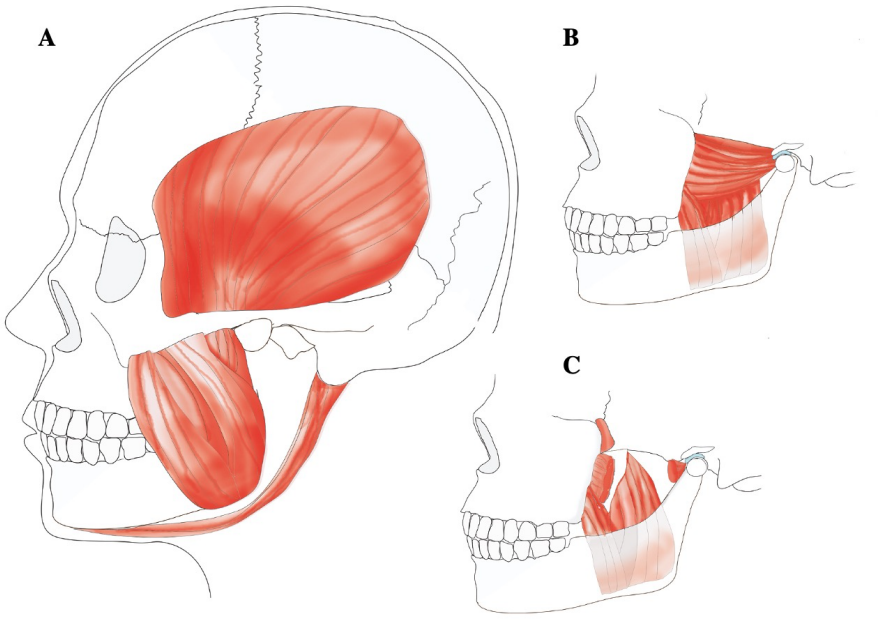

Figure 2A-2C; The major muscles which control jaw closing include the M. masseter, M. pterygoideus medialis, and M. temporalis (A and C). The mandibular condyle is positioned in the glenoid fossa of the temporal bone with the articular disc in centre when the jaw is closed. The disc separates and provides a biomechanical and functional support for the bone components. The major muscles that control the jaw opening include the M. pterygoideus lateralis, M. suprahyoideus, M. geniohyoideus, M. mylohyoideus, and M. digastricus (A and B). When opening, the mandibular condyle rotates within the articular fossa, mainly through the action of the M. pterygoideus lateralis (B). After the rotation, the mandibular condyle continues anterior and inferior translational movement down along the articular eminence through the action of the M. pterygoideus lateralis. The condyle can move in several directions: translational, lateral, slide bilateral anterior, or unilateral anterior with the opposite condyle moving posterior.

The disc initially moves anteriorly with the movement of the condyle, and then with progressive translational movement of the condyle, the disk moves posteriorly over the condyle to support the whole opening process. The TMJ opening functions in chewing, swallowing, phonetics, maintenance of correct air pressure, breathing, and facial expressions (Bordoni 2021; Scrivani et al. 2008).

1.5.2 Articular Disc Displacement

Anterior displacement of the articular disc is generally common, including in healthy, pain-free individuals. The disc displacement is often with reduction, and it often creates a ’click’ when the jaw is closing, which means the disk glides back over the condyle head. Sometimes the noise may be accompanied by pain, called ‘painful clicking’ (PC) (Poluha et al. 2019). Anterior disk displacement can also be without reduction, which means the disc will stay in front of the condyle when the jaw closes, often referred to as chronic closed lock (CCL) (Al-Baghdadi et al. 2014).

1.5.3 Trigeminal Nerve

The trigeminal nerve (V) is responsible for the somatosensory perception, including pain, of the major part of the face, mouth, and facial muscles, and also motor function of the masticatory muscles. The nerve origin is in the brainstem, from whence it goes to the trigeminal ganglion where it is divided into three branches: the ophthalmic branch (V_1), the maxillary branch (V2), and the mandibular branch (V3). The three branches divide the face into three separated sensory dermatomes (Goellner and Rocha 2020; Terrier et al. 2021).

1.6 Pain

1.6.1 Basics of Pain

The definition of pain from The International Association for the Study of Pain (IASP) is: 'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (Raja et al. 2020). The primary types of pain are: 1) nociceptive pain, 2) inflammatory pain, and 3) neuropathic pain. Nociceptive pain occurs as a response to a noxious stimulus in periphery neurons (Coghill 2020). The noxious stimuli that induce the action potential in the periphery neurons may be mechanical, thermal, or chemical, and is transmitted through the spinal cord to the CNS. The intensity of nociceptive stimulus is based on both the number of involved neurons and the frequency of the action potential (Coghill 2020). The nociceptive pain system is highly represented at several CNS levels, and its signals can hardly can be disrupted (Coghill 2020). Inflammatory pain occurs when nociceptive pain pathways are activated as an inflammatory or immune response. The noxious stimulus in inflammatory pain is triggered by inflammatory mediators, like cytokines and prostaglandins, released from the immune cells. Pain is one of the five classic symptoms of inflammation. The other four are: redness, swelling, heat, and loss of function (Vasko 2009). Neuropathic pain is a result of pathology in the neural system, which may involve peripheral or central sensitization mechanisms (Campbell and Meyer 2006). Examples of causes of neuropathic pain can be nerve compression, nerve trauma, or autoimmune diseases (Campbell and Meyer 2006). Inflammatory and neuropathic pain share some of the same mechanisms, including elevated expression of cytokines and cytokine receptors. However, the resolution of pain and response to pharmaceutical treatment is different (Xu and Yaksh 2011).

1.6.2 Pain in TMD

In TMD, there is a poor correlation between the patients' subjective pain intensity and evidence of tissue damage (Cairns 2010; Fricton 2007). TMD-related pain is more likely the result of altered central sensitization of pain, together with contributing behavioural and psychosocial factors (Cairns 2010; Sagripanti and Viti 2018). Central sensitization

has previously been described as an increase in synaptic efficiency in somatosensory CNS pathways at the same time as inhibitory pathways are suppressed, and the result is nociceptive hypersensitivity (hyperalgesia) (Woolf 2011). Hyperalgesia has also been discussed as an important characteristic in general chronic pain, including orofacial pain and TMD (Curatolo et al. 2015; Sagripanti and Viti 2018). TMJ pain in the presence of TMJ degenerative disease is better understood (Cairns 2010). Afferent nociceptors in the TMJ can be activated by a noxious stimulus, e.g., inflammatory mediators, and lead to the experience of pain (Sessle 2005; Yi et al. 2021). Animal models have shown that TMJ inflammation can activate both glial and immune cells in the trigeminal ganglia and the spinal trigeminal nucleus (Villa et al. 2010). Still, some individuals with TMJ disc displacement and TMJ degenerative disease are pain free, while others with no evidence of TMJ pathology experience high pain intensity (Cairns 2010).

1.6.3 Possible Pain Modulators

Several pain-related modulators have been discussed as having a role in TMD-related pain. Inflammatory mediators as cytokines, including IL-1β, TNF-α, IL-6, NGF, neurotransmitters, and neuropeptides including substance P and serotonin (5HT), have been suggested to play an important role in altered sensitization in patients with TMD (Asakawa-Tanne et al. 2015; Kopp 1998; Yi et al. 2021). Previous studies have shown that elevated IL-1β in the TMJ synovial fluid from TMJD patients was highly associated with hyperalgesia and amplified inflammation in the TMJ (Asakawa-Tanne et al. 2015; Kopp 1998). Also, elevated concentration of TNF-α, IL-6, and 5HT have been revealed in studies of synovial fluid from TMJD patients (Güven et al. 2015; Kopp 1998). Inflammatory mediators also activate TRPV1 channels, which are responsible for the neurotransmission of the pain stimulus, and their expression and activity is important in hyperalgesia (Levine and Alessandri-Haber 2007). Results from animal studies have indicated that estradiol can also modulate TMJ pain and inflammation, along with increased expression of TRPV1 channels in the hippocampus (Wu et al. 2010). The prevalence of TMD is much higher in women compared to men, and estradiol could be one of the contributing factors (Cairns 2010). Individuals with genetic variants of the gene encoding catecholamine-O-transferase, which are associated with higher pain

sensitivity, have also been identified with a higher risk of developing TMD (Diatchenko et al. 2006; Diatchenko et al. 2005).

1.7 Stress and Cognition

1.7.1 Basics of Stress

The stress response centre lies in the hypothalamus, where corticotropin-releasing hormone (CRH) is released as a response to a stress stimulus (Chrousos and Gold 1992). The release of CRH is also the first step in the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which through a cascade leads to enhanced secretion of glucocorticoids, including cortisol, from the adrenal cortex (Smith and Vale 2006). Noradrenaline, which is a catecholamine, coordinates the somatic arousal of the stress response, and is simultaneously released from the locus coeruleus (LC) in the brain (Bangasser and Valentino 2012; Gameiro et al. 2006). Both glucocorticoids and catecholamines induce a specific response in every cell in the body. The complex interplay has an effect on the regulation of several other neurotransmitters including substance P, dopamine, and 5HT, which are involved in both stress response and pain modulation (Chrousos 2009; Gameiro et al. 2006). Altogether, the stressful response may affect major CNS systems including the mesocorticolimbic dopaminergic system, the amygdala, and the hippocampus, which in turn may have an effect on behavioural, endocrine, visceral, autonomic, and immune responses (Chrousos 2009; Gameiro et al. 2006).

1.7.2 Stress in TMD

A stressful behaviour pattern is thought to have a significant role in the development and maintenance of TMD-related dysfunction and pain (Cairns 2010; Fricton 2007; Gameiro et al. 2006). Psychosocial factors, including stress and depression, have been previously associated with TMD (Fillingim et al. 2011; Hoffmann et al. 2011; Slade et al. 2016). Significantly higher concentrations of cortisol in patients with TMD compared to healthy individuals have been demonstrated in several studies (Chinthakanan et al. 2018; Da Silva Andrade et al. 2008; Korszun et al. 2002; Salameh et al. 2015; Staniszewski et al.

2018). The observed high concentrations of cortisol in TMD patients might be a result of psychological stressors, which alter the reactivity of the HPA axis (de Leeuw et al. 2005; Gameiro et al. 2006; Staniszewski et al. 2018). The LC-noradrenaline system has also been discussed to be more reactive in women, and may increase the risk of developing stressful disorders (Bangasser and Valentino 2012). Additionally to neuroendocrinological effects, psychosocial stress might also induce muscular tension and oral parafunctions with accompanying pain (de Leeuw et al. 1994; Fricton 1999; Gameiro et al. 2006).

1.7.3 Neurocognitive Function

Neurocognitive function is a complex and theoretical concept which encompasses several domains, such as memory, executive function, and attention. Each of these domains includes multiple aspects (Hammar et al. 2022). Executive function (EF) refers to a set of neurocognitive processes that regulate behaviour, affects, and thoughts (Anderson 2008). Cognitive inhibition is one aspect of EF, and based on the Stroop effect (Stroop 1935), it is defined as 'the stopping or overriding of a mental process, in whole or in part, with or without intention' (Friedman and Miyake 2004; Friedman and Robbins 2022; Macleod 2007). The Stroop test is a cognitive assessment tool that evaluates the capacity to inhibit or interrupt an automated skill (in this case reading) and serves as a measure of prepotent response inhibition, which is the ability to deliberately suppress dominant or automatic responses. Cognitive functioning, including EF, can also be evaluated through self-report measures; however, most studies indicate limited correlation between standardized test measures and self-report measures (Friedman and Gustavson 2022). Both these aspects of EF contribute to daily functioning. Therefore, utilizing both objective performance-based tasks like the Stroop test and subjective self-report measures can provide valuable insights in studies related to neurocognitive functioning in individuals with TMD.

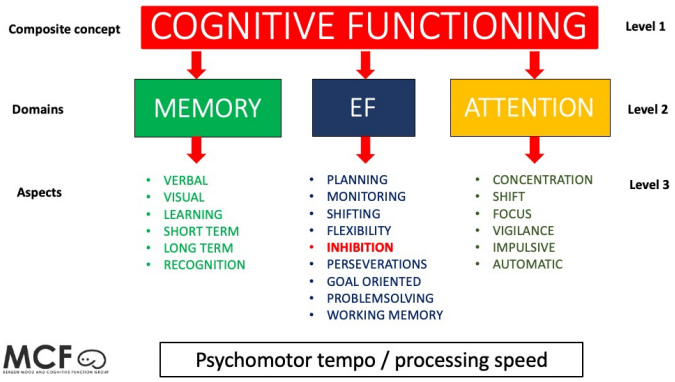

Figure 3; This figure presents a theoretical model of cognitive function, with three main domains and several aspects within each domain (Hammar et al. 2022) (Printed with permission from author).

1.7.4 Psychosocial Factors in Relation to Pain

Based on the outcome from a review, it has been suggested that patients' emotional state may have a significant effect on the experience of pain, through modulation of neuroendocrine and peripheral factors (Heir 2019). Pain may affect mood, behaviour, and emotions, and result in homeostatic disruptions of the somatosensory system over time (Craig 2003). Chronic pain often occurs simultaneously with depression where both factors reinforce each other, also suggesting a neurobiological association (Li 2015). A similar association with persistent stress has been discussed to affect neuronal pathways, resulting in hyperalgesia in chronic pain (Jennings et al. 2014; Li 2015). Noradrenaline is involved in both stress response and complex pain modulation at several levels (Pertovaara 2006). Poorer EF, as shown by neurocognitive tests, has previously been suggested as a risk factor for developing chronic pain, in a longitudinal study of patients after knee or breast surgery (Attal et al. 2014). Limited research has explored the associations between EF and chronic pain, particularly in conditions beyond

more generalized conditions such as fibromyalgia (Berryman et al., 2014), and only one has specifically focused on patients with TMD (Weissman-Fogel et al. 2011). In this study, involving 17 female patients with TMD and matched controls, slower response times were observed in the TMD group during a Stroop task (Weissman-Fogel et al. 2011).

1.8 Diagnostics

1.8.1 Development of Evidence Based Diagnostics

Standardized diagnostics of TMD today have been developed by the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin and LeResche 1992). The (RDC/TMD) consists of two components: the Axis I and Axis II. The Axis I includes screening and differentiation of pain-related TMD and TMJD, and Axis II is used for assessment of jaw function and psychosocial factors. The (RDC/TMD) also divides TMD in Axis I into three main categories: 1) myofascial myalgia, 2) TMJ disc displacement, and 3) other joint conditions (e.g., TMJ inflammation, arthrosis). A new evidence-based version of Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), including the Axis I and Axis II from RDC / TMD, has been validated for clinical and research use (Schiffman et al. 2014b). The DC/ TMD were additionally based on a newer biopsychosocial model of pain, where biological and psychological factors affect each other and have to be evaluated simultaneously (Loeser 2000). For clinical use in Norway, the Norwegian Directorate of Health has developed its own version of national Norwegian guidelines for diagnostics and treatment of TMD, which are evidence based and are close to a modified version of the DC/ TMD (Helsedirektoratet 2016).

1.8.2 Clinical Examination

To achieve patient compliance, it is important to have enough time for the clinical examination to establish a good patient-therapist relationship, which may have a significant role in later management of the patient (Hirsh et al. 2005).The clinical examination and registration should include: anamnesis (including pain intensity and

duration, psychosocial factors, previous trauma, and medical status), inspection of the oral cavity and teeth, intra- and extra-oral muscle palpation, head and neck symmetry, other TMD related symptoms, TMJ function and sounds, and oral parafunctions (Helsedirektoratet 2016; Schiffman et al. 2014b). Radiologic images may be needed for diagnostic purposes. An orthopantomogram (OPG) is often adequate; however, the need for advanced radiographic images such as MRI has to be evaluated individually (Helsedirektoratet 2016; Lobbezoo et al. 2004; Xu-chen 2001).

1.8.3 TMD Related Diagnoses

Even though TMD can consist of several conditions, the general ICD-10 code for TMD is K07.6 Temporomandibular joint disorders. A significant number of TMD patients experience myofascial myalgia (Lobbezoo et al. 2004). TMJ disc displacement with or without reduction, and TMJ inflammatory disease may occur simultaneously (Helsedirektoratet 2016; Lobbezoo et al. 2004; Tanaka et al. 2008). Other common TMD-related diagnoses includes arthralgia, temporal tension headache, and hypermobility (Helsedirektoratet 2016; Ögren et al. 2012). Frequent comorbidity, especially with other non-TMD pain-related disorders (e.g., irritable bowel syndrome, and fibromyalgia), are also more frequently observed in TMD patients compared to healthy individuals (Hoffmann et al. 2011). TMJ ankylosis may be observed in some severely affected TMJD patients, leading to impaired joint movement, when the TMJ fuses into a fibrous tissue or bone, or a combination of these two (Shivakotee et al. 2020).

1.8.4 Differential Diagnoses

The most common differential diagnoses for TMD are related to odontogenic conditions including caries, pulpitis, pericoronitis, apical periodontitis, osteomyelitis, and odontogenic sinusitis (Helsedirektoratet 2016; Kumar and Brennan 2013). Other more and less common differential diagnoses includes headache, hereunder: tension headache, migraine and cluster headache, and neuropathic pain such as: trigeminus neuralgia, glossopharyngeal neuralgia, postherpetic neuralgia, and atypical odontalgia (Helsedirektoratet 2016; Kumar and Brennan 2013; Siccoli et al. 2006). Sinus and ear-

related symptoms might also mimic TMD symptoms (Helsedirektoratet 2016; Kumar and Brennan 2013). Be aware of red flags such as metastasis (previous cancer), infection (fever, swelling), recent head trauma, intracranial pathology, vision disturbances, acute high intensity pain, and temporal arthritis (Durham et al. 2015; Helsedirektoratet 2016; Kumar and Brennan 2013; Siccoli et al. 2006). These conditions are relatively rare but must be taken seriously, and individually evaluated with the right professional consultancy when necessary (Helsedirektoratet 2016; Kumar and Brennan 2013; Siccoli et al. 2006).

1.9 Treatment

1.9.1 Conservative Treatment

Conservative, non-invasive treatment is preferred, and should always be tried first, in management of TMD. Recommended conservative treatment of TMD includes adequate patient information, jaw muscle exercises, relaxation exercises, sometimes an occlusal splint, and/or NSAIDs (Dworkin et al. 1994; Helsedirektoratet 2016; Lindfors et al. 2020; Scrivani et al. 2008). Jaw exercises have been shown to effectively reduce TMD-related pain and headache (Lindfors et al. 2020), and are designed to increase muscular function, induce relaxion, and regain maximal jaw opening capacity (McNeely et al. 2006). Occlusal splint is one of the most frequent treatments of TMD with the purported purpose of inducing the relaxation of masticatory muscles and reducing the mechanical load on the TMJ (Wänman 2016). The treatment with an occlusal splint is non-invasive and reversible, and has shown to be an effective treatment for TMD (Wänman 2016; Zhang et al. 2020). Psychologically-related disorders and other non-TMD pain-related symptoms should be treated simultaneously, as they will have an effect on the TMD treatment prognosis (Helsedirektoratet 2016; Zakrzewska 2013). Cognitive behaviour therapy might be successful in treatment of contributing factors such as anxiety, depression, and sleep disorders (Fricton 2007). Patients may also be anxious regarding their TMD symptoms. Therefore, it is crucial to educate patients that TMD symptoms are typically temporary and rarely indicative of a serious illness. With conservative

treatment, the majority of TMD patients are likely to experience recovery. (Durham et al. 2015; Helsedirektoratet 2016).

1.9.2 Treatment by Multidisciplinary Team

Patients with long-term TMD, especially in the presence of several TMD-related diagnoses, and also other pain disorders, as well as psychological disorders, might need multidisciplinary treatment (Zakrzewska 2013). Since TMD is a complex disorder, a simultaneous and coordinated bio-psychosocial treatment approach by a multidisciplinary team may provide a successful treatment of TMD (Ahmed et al. 2014; Garrigós-Pedrón et al. 2019). A multidisciplinary team should include medical specialists, psychologists, physiotherapists, and dental specialists who collaborate in diagnosis and treat the patient simultaneously (Ahmed et al. 2014). Treatment of TMD by a multidisciplinary team may be effective in order to reduce long-term TMD symptoms, and has shown to secure correct diagnoses, provide adequate patient information regarding their disorder, and improve patients' satisfaction with treatment (Ahmed et al. 2014; Nilsson et al. 2013).

1.9.3 Pharmaceutic Treatment

Previously, it has been common to treat painful, recurring TMD with opiates, muscle relaxants, and tricyclic anti-depressants (Fricton 2007). However, the evidence for the clinical effect of such pharmaceutics is poor (Cascos-Romero et al. 2009; List et al. 2003; 2004; Wänman 2016). The initial treatment of TMD may include paracetamol and NSAIDs, and should be limited to one week of use (Helsedirektoratet 2016; Wänman 2016). Treatment with paracetamol and NSAIDs has shown low to moderate pain-relieving effect for TMD pain (List et al. 2003). Opioids may provide pain relief; however, they are not recommended for treatment of TMD due to the consequences of adverse effects (Wänman 2016).

1.9.4 TMJ Intraarticular Injections

Injections can be performed directly into the TMJ, both into the superior and inferior cavity (Li et al. 2012). Injections with corticosteroids or hyaluronic acid can be a treatment option for patients with TMJ arthritis, and have been shown to possibly reduce

pain, and sometimes restore maximum jaw opening capacity (Bjornland et al. 2007; Li et al. 2012). Nerve blocks with local anaesthetics (e.g., lidocaine) can also be used for diagnostics, or to reduce pain quickly(Danzig et al. 1992).

1.9.5 Surgical Treatment

Recurring TMD symptoms, especially including disabling pain and jaw opening limitation, in patients with TMJ disorder (TMJD), where conservative treatment has proven to be inadequate, may need to be treated surgically (Helsedirektoratet 2016). In the case of inflammatory TMJD, arthrocentesis is a minimally invasive treatment with the purpose of flushing out inflammatory mediators from the TMJ, which may reduce pain intensity and TMJ sounds, and increase maximal jaw opening (Bergstrand et al. 2019; Nitzan et al. 2016; Sahlström et al. 2012). Arthroscopic lysis and lavage is an effective treatment for jaw opening limitation as in CCL, and may restore function and reduce pain (Abboud et al. 2015; Breik et al. 2016; Holmlund et al. 2001). The therapeutic effects of lysis and lavage primarily stem from the irrigation and flushing of the joint cavity, stretching of the capsule, mobilization of the articular disc, and disruption of adhesions within the joint (Nitzan et al. 1990; Nitzan and Lehman Naaman 2017). Arthrocentesis and arthroscopy are surgical techniques that can be performed under local anaesthesia.

TMJ arthroplasty is only recommended for a very low percentage of all TMJD patients with severe TMJ damage. There are several surgical techniques for the treatment of severe non-resolving TMJD. Discectomy, with or without graft replacement, is a treatment options for patients with articular disc displacement, particularly in CCL (Bjørnland and Larheim 2003; Holmlund et al. 2013; Holmlund et al. 2001). In those patients, discectomy has shown to effectively reduce pain and restore function (Bjørnland and Larheim 2003; Holmlund et al. 2013; Holmlund et al. 2001). However, the technique is more invasive compared to lysis and lavage (Holmlund et al. 2001). Transversal gap osteotomy might be an effective treatment of TMJ ankylosis and reshaping the TMJ to a functional position (Mounir et al. 2020; Parmar et al. 2015). The available modern technique for gap osteotomy can be performed by a computer-guided

surgical procedure (Mounir et al. 2020). Sagittal ramus condylotomy is an alternative treatment, more invasive compared to gap osteotomy (Parmar et al. 2015), but with the advantage that the joint will be spared. A temporal muscle flap can be used for reconstruction of the articular disc after discectomy, and this is considered a safe and effective treatment (Moreau et al. 2018; Shivakotee et al. 2020). The bony compartments of the TMJ can also be reconstructed by using bone grafts or alloplastic materials (MacIntosh 2000; Moreau et al. 2018). In worst cases of TMJ degenerative disease or ankylosis, when there is no effect from other treatments, a total TMJ reconstruction with alloplastic materials might be an option (Moreau et al. 2018; Neelakandan et al. 2014).

1.10 Prognosis and Consequences

1.10.1 Individual Prognosis

TMD symptoms are often temporary and may resolve with adequate information and supervision of the patient (Berge et al. 2016; Helsedirektoratet 2016). However, a minor proportion of TMD patients evolve into a long-term state with high intensity pain, which in turn leads to significant social, emotional, and functional disability (Berge et al. 2016). Comorbid psychological disorders worsen the TMD prognosis and may result in a poorer treatment outcome (Jung et al. 2021; Zakrzewska 2013). A previous longitudinal study of TMD patients associated higher pain intensity, and several pain related conditions, with poorer probability of TMD pain relief (Forssell et al. 2017). Similarly, higher frequencies of facial pain as well as increasing numbers of painful body sites in TMD patients were associated with poorer treatment outcome (Rammelsberg et al. 2003). Longer pain duration has also been associated with poorer prognosis of pain relief in general chronic pain (Landmark et al. 2018).

1.10.2 Professional TMD Management

Several systematic reviews of TMD highlight the lack of evidence for how to base management decisions (Fricton et al. 2010; Mujakperuo et al. 2010). One of the reasons could be a lack of standardized and validated evidence-based education in management of TMD for health professionals (Klasser and Gremillion 2013). In Norway, the

Norwegian evidence-based national guidelines in management of TMD are published online (Helsedirektoratet 2016). However, it is uncertain to what extent the guidelines are known by the Norwegian dental and medical healthcare professionals. There is also no natural platform in the healthcare system for patients with TMD, and this leads to detrimental and purposeless consultations within dental and medical care without patients getting a solution for their complaints due to sparse communication. There is also minimal collaboration between the involved healthcare systems. Treatment of chronic pain in general is challenging, and traditional treatment options have failed to effectively reduce pain intensity or improve psychological and functional variables in such patient populations (Turk et al. 2011). The scientific approach to chronic pain during the past decades has switched from a direct linear association with tissue damage to a multifactorial etiology including several psychosocial factors (Turk et al. 2016). An appropriate goal might be to individualize clinical pain management for each patient, and to achieve proper interdisciplinary communication between health professionals.

1.10.3 Consequences for society

Myofascial pain has been one of most frequent types of muscular pain for decades (Fricton et al. 1985). Musculoskeletal disorders, including TMD, generate severe consequences in the Western world, making patients suffer and affecting society and professional healthcare systems in an economic and resource-intensive way (Landmark et al. 2018; Turk 2002). A significant number of chronic TMD patients with high intensity pain have ended up unemployed or with a working disability (Berge et al. 2016), generating an economic expense for the government. An efficient improvement in managing chronic pain, including that of TMD, would relieve both economic and social resources in Western countries.

1.11 TMD Patients in Norway

About one decade ago, the Norwegian TMD Patient Association (TMD Foreningen) claimed that treatment and diagnostics of TMD was not adequate in Norway, and that

TMD patients were not taken seriously. Several TMD patients went abroad to private clinics in the UK, Germany, and the USA, and funded their own treatments, which could cost up to 600,000 NOK. The majority of those treatments lacked scientific documentation, and had limited effect. The Norwegian TMD Patient Association got politically involved and started a debate, which in turn ended in the year of 2013, when the Norwegian Directorate of Health assigned Haukeland University Hospital in Bergen (HUH) the task of launching a multidisciplinary evaluation programme for TMD patients (Berge et al. 2016). The multidisciplinary programme for TMD patients at HUH, included specialists in maxillofacial surgery, TMD/orofacial pain, orthodontics, radiology, and the Centre for Pain Management and Palliative Care (a pain clinic, including one psychologist, one anesthesiologist, and one physiotherapist). A collaboration with the Oral and Maxillofacial Pain Center at the Massachusetts General Hospital in Boston, USA was also initiated during the development of the multidisciplinary programme. The mission of the multidisciplinary team was to: 1) launch a national evaluation programme for refractory TMD, 2) establish evidence based national guidelines for treatment of TMD, and 3) establish a national treatment centre for non-resolving orofacial pain (Berge et al. 2016). The present thesis is based on data from the TMD patients in the multidisciplinary evaluation programme of TMD patients at HUH. The Norwegian national guidelines for treatment of TMD were published by the Norwegian Directorate of Health in 2016 (Helsedirektoratet 2016). The National Unit for Orofacial Pain (Nasjonal Behandlingstjeneste for Uavklarte Ansikt- og Kjevesmerter (NBT) was established at HUH in 2018.

2. Aims

The overall aim of this thesis was to characterize the group of patients with painful TMD (pTMD) in order to improve treatment. developing preventive and early treatment for a better quality of life.

Specific aims

Paper I (Study Ia): *The aim* of this controlled cross-sectional study was to assess the stress levels and HPA axis activity in pTMD patients compared to healthy individuals, based on self-reported psychosocial-related questionnaires and the concentration of cortisol in saliva. *The hypothesis* was that pTMD patients have an upregulated HPA axis.

Paper II (Study Ia): *The aim* of this controlled cross-sectional study was to evaluate essential proteins, hormones, electrolytes, and vitamins in blood from pTMD patients. *The hypothesis* was that pTMD patients have systemic disease, malnutrition, and systemic inflammation.

Paper III (Study Ib): This was a longitudinal study of patients with pTMD who had been examined by a multidisciplinary team at HUH three years ago. *The general purpose* was to identify risk factors of non-resolving pTMD, which may indicate the need for early prevention and treatment of patients. *Specific* purposes were to assess patients' TMD symptoms, physical function, and psychosocial variables, and patients' satisfaction with treatments proposed by the multidisciplinary team. *The hypothesis* was that there are specific risk factors that may significantly affect the outcome of the TMD treatment.

Paper IV (Study II): *The main aim* of this controlled cross-sectional study was to investigate cognitive inhibition, self-perceived cognitive functioning, rumination, depression, and quality of life (QoL) in patients with pTMD, compared to healthy subjects in relation to pain and how to master chronic pain. *Our hypothesis* was that: 1) neurocognitive inhibition is poorer in pTMD, and 2) self-perceived cognitive functioning and QoL is poorer in pTMD-patients compared to healthy controls. In addition,

rumination and depression are higher and these factors are related to pain and the ability to master chronic pain.

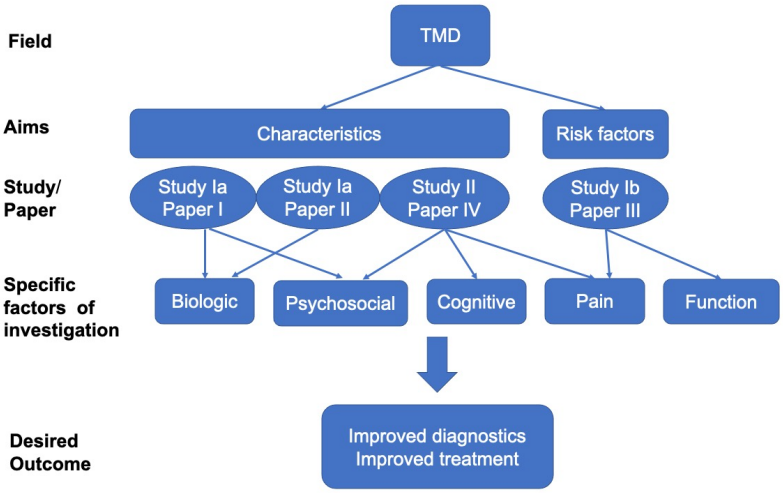

Figure 4; A presentation of study aims, investigation, and desired outcome.

Table 1: Overview of thesis and papers.

Title of the thesis	*Biological markers and cognitive function in painful temporomandibular disorder.*			
Main aims of the thesis	To characterize the group of patients with painful TMD (pTMD) in order to develop preventive and early treatment of pTMD to prevent chronic pain and disability.			
Studies	**Study Ia**		**Study Ib**	**Study II**
Title of papers	**Paper I:** Temporomandibular Disorders Related to Stress and HPA Axis Regulation	**Paper II:** Serum Analysis in Patients with Temporomandibular Disorders: A Controlled Cross-Sectional Study in Norway	**Paper III:** High Pain Intensity is a Risk Factor for Non-Resolving TMD: A Three-Year Follow-Up of a Patient Group in a Norwegian Interdisciplinary Evaluation Programme	**Paper IV:** Neurocognitive Functioning in Patients with Painful Temporomandibular Disorders
Journal (year)	*Pain Research and Management* (2018)	*Pain Research and Management* (2019)	*Journal of Pain Research* (2022)	*Journal of Pain Research* (Submitted 2023)
Aims of papers	To assess the stress levels and indication of HPA axis activity in pTMD patients, based on cortisol and cortisone levels in saliva and scores for self-reported, psychosocial-related questionnaires.	To evaluate essential proteins, hormones, electrolytes, and vitamins in serum from TMD patients.	To investigate the outcome of patients with long-term refractory pTMD three years after a Norwegian interdisciplinary evaluation programme with attention to patient satisfaction, function, pain, and psychosocial variables.	To investigate psychosocial and neurocognitive factors in pTMD which could have consequences in mastering chronic pain.
Research questions	1) Are cortisol and cortisone concentrations in saliva significantly higher in pTMD patients, indicating elevated HPA axis activity? 2) Are psychological related scores from CSQ and HADS significantly higher in pTMD patients?	1) Do pTMD patients have systemic disease, malnutrition, and systemic inflammation, which can be shown by analyses of blood samples? 2) Can blood samples be used as a biomarker or as a diagnostic tool in pTMD?	1) Are there any risk factors for non-resolving pTMD? 2) Which factors are significantly related to improvement of pTMD symptoms?	1) Is neurocognitive performance measured with CWIT significantly poorer in patients with pTMD compared to controls? 2) Are self-reported cognitive function and QoL poorer, and are rumination and depression higher in pTMD patients compared to controls?
Design	Controlled cross-sectional study	Controlled cross-sectional study	Longitudinal study	Controlled cross-sectional study
Participants	44 out of 60 pTMD patients from Study I	60 pTMD patients and 60 controls from Study I	39 out of 60 pTMD patients from Study I	(Extended pTMD population from Study I) 22 out of 129

				pTMD patients and 19 controls from Study II.
Measures	**Biological:** cortisol and cortisone in saliva. **Questionnaires:** CSQ, HADS	**Biological:** 19 different determinants in blood samples.	**Questionnaires:** CSQ, GPI, HADS, MFIQ, RMS.	**Cognitive**: WASI, D-KEFS: CWIT. **Questionnaires:** GPI**,** MADRS-S, OHIP-TMD, PDQ, RRS, RRQ.
Statistical Methods	Paired sample *t*-test, Wilcox matched test, linear multi-regression, linear correlation.	Paired sample *t*-test, linear correlation.	Wilcox matched test, Kruskal Wallis test with a post hoc Dunn test, logistic regression.	Wilcox rank-sum test.
Main findings	1) Cortisol and cortisone concentrations in saliva were significantly higher in pTMD patients compared to controls. 2) CSQ and HADS scores were significantly higher in pTMD patients compared to controls.	1) The results could not associate any severe systemic disease, malnutrition, or systemic inflammation with pTMD. 2) Results did not suggest that serum analyses should be used as a biomarker or diagnostic tool of pTMD.	1) High pain intensity at baseline was a significant risk factor for poorer recovery. 2) Improved coping with TMD pain included decreased pain intensity, and CSQ and MFIQ scores.	1) The tested neurocognitive performance with CWIT in the pTMD group was equal to the control group. 2) The pTMD patients reported significantly more self-perceived cognitive difficulties, higher rumination, more depressive symptoms, and lower QoL compared to healthy controls.
Conclusion thesis	The pTMD patients in our study suffered from high levels of psychosocial stress, including anxiety, depression, rumination, pain-related catastrophizing, and low QoL related to oral health. The pTMD patients also suffered from high pain intensity and self-perceived cognitive deficits compared to a healthy control group. Higher pain intensity was associated with poorer pain relief and subjective improvement of TMD over time, and was considered as an important risk factor for recovery from pTMD. The results indicate that the above psychosocial factors could be targeted in treatment and interventions for pTMD patients.			

Note: Coping Strategies Questionnaire (CSQ), Color Word Interference Test (CWIT), Delis-Kaplan Executive Function System (D-KEFS), General Pain Index Questionnaire (GPI), Hospital Anxiety Depression Scale (HADS), Montgomery Åsberg Depression Rating Scale (MADRS), Mandibular Function Index Questionnaire (MFIQ), Oral Health Impact Profile – TMD (OHIP-TMD), painful temporomandibular disorder (pTMD), Roland Morrison Scale (RMS), Rumination Reflection Questionnaire (RRQ), Ruminative Response Scale (RRS), Temporomandibular Disorder (TMD), Weschler Abbreviated Scale of Intelligence (WASI).

3. Materials and Methods

3.1 Study Background and Design

In 2013, the Norwegian Ministry of Health assigned a national multidisciplinary evaluation programme for TMD patients at Haukeland University Hospital (HUH) in Bergen, Norway (Berge et al. 2016). The present thesis was based on research from the national TMD project at HUH. Study Ia and Study II (Paper I, II, & IV) were clinical- and questionnaire-based, controlled cross-sectional studies. Study Ib was a longitudinal questionnaire-based, three-year follow-up study of TMD patients.

3.2 Study Population in Study I (Paper I, II & III)

Study Ia included Paper I and Paper II. Study Ib included Paper III. Study I was based on a study population consisting of 60 painful TMD (pTMD) patients, all affected with refractory TMD symptoms, and 60 healthy age- and sex-matched control subjects. The patients with pTMD were referred by their general medical practitioner (GMP) to the National TMD project from various health regions in Norway between 2013 and 2015, for comprehensive assessment by the multidisciplinary team, and were sequentially enrolled in the study. The inclusion criteria were adults aged 18 years or older who had experienced long-term TMD-related pain, in addition to a referral from their GMP. The patients included in the study were diagnosed by the multidisciplinary team in accordance with a beta version of the TMD guidelines from the Norwegian National Health Directorate, which were subsequently published in 2016 (Helsedirektoratet 2016), and align with the diagnostic criteria included in the Diagnostic Criteria for TMD (DC/TMD) (Schiffman et al. 2014a). Exclusion criteria were non-TMD-related orofacial pain, drug dependence problems, obvious psychiatric diagnoses, and unresolved economic disability claims. A control group was recruited for comparison with the pTMD patients in Study Ia during 2016. A majority of the control group consisted of employees and students from the Department of Clinical Dentistry at the University of

Bergen, who were not affiliated with the study research group. The remaining members of the control group were recruited from the general population in Bergen, Norway. Inclusion criteria for the control group was age 20 years or older and age- and sex-matched with the TMD patient group. Exclusion criteria were TMD symptoms or other musculoskeletal pain, and symptoms in the head and neck area. Paper I (Study Ia) included 44 out of 60 pTMD patients, and 44 healthy age- and sex-matched control subjects. Paper II (Study Ia) included all 60 pTMD patients and 60 controls. In Paper III (Study Ib), 39 out of 60 TMD patients answered the questionnaires at follow-up.

3.3 Study Population in Study II (Paper IV)

Paper IV (Study II) included an extended population of pTMD patients from the National TMD project at HUS. The inclusion criteria were the same as for Study Ia and Ib, and the original patient population of 60 pTMD patients was extended to 129 patients during the years 2015-2018. A new control group was recruited for Study II. The control group was randomly selected using, as far as possible, the Norwegian National Population Register (Folkeregisteret), invited by mail to participate in the project, and further recruitment was facilitated through acquaintances of the research group. The control group was matched with the pTMD patients for age, gender, and educational level. The inclusion criteria for the control group in Study II were the same as for Study Ia. The exclusion criteria were TMD symptoms or other musculoskeletal pain, and symptoms in the head and neck area, (colour) blindness, and poor skills in Norwegian language.

3.4 Ethics

Ethical approval was granted by the Regional Ethical Review Board Southeast (2015/930) for Study Ia (Paper I and Paper II), and (2018/647) for Study Ib (Paper III) and Study II (Paper IV), in accordance with the Helsinki Declaration (1964). The present thesis builds upon previous research conducted within the multidisciplinary evaluation

programme at HUH. A written informed consent was received from all subjects, including TMD patients and healthy controls, who participated in the study.

3.5 Clinical Examination

At the first evaluation of pTMD patients, a clinical examination was performed by the multidisciplinary evaluation team at HUH. Six different specialists examined the patients: an oral and maxillofacial surgeon, a specialist in orofacial pain and TMD if necessary, a specialist in orthodontics, a pain physician, a physiotherapist, a clinical psychologist, and a physician specialized in radiology. At the final consultation, the results of the assessment were presented to the patient along with an explanation of why they were in pain followed by treatment suggestions, which were discussed with the patients. The suggested treatment plan was reported to their general medical practitioner (GMP) for follow up. The control group underwent a simplified clinical examination performed by one dental specialist to exclude any TMD symptoms. The clinical examination of control subjects included masticatory muscles palpation and assessment of TMJ function.

3.6 Saliva Samples (Paper I, Study Ia)

Saliva samples were collected in the morning with the Salivette Cortisol Code Blue test kit (Sarstedt Darmstadt, Germany) and stored at −80°C until analysis. Cortisol and cortisone were determined by liquid chromatography–tandem mass spectrometry (LC-MS/MS) at the Core Facility for Metabolomics, University of Bergen. Sample processing was completely robotized (Hamilton Robotics, Inc., Reno, NV, USA). Briefly, 20 µL of internal standard (Cortisol-2,3,4-$^{13}C_3$) was added to 100 µL of human saliva, which was subjected to liquid–liquid extraction with 480 µL of ethylacetate–heptane (80:20, v/v). The supernatant (380 µL) was subsequently washed with 50 µL of sodium hydroxide (0.1 M). Next, 280 µL of supernatant was removed and evaporated to dryness under nitrogen flow and then reconstituted in 100 µL of a 0.01% aqueous

solution of formic acid: methanol (50:50, v/v). Samples were then analyzed on a Waters Acquity UPLC system connected to a Waters Xevo TQ-S tandem mass spectrometer (Waters, Milford, MA, USA). The compounds were separated on a C-18 BEH phenyl column from Waters (100 × 2.1 mm column, 1.7-mm particle size), which was developed by gradient elution over 5.5 min, using an aqueous solution of formic acid and acetonitrile as mobile phases. Formic acid adducts were detected in negative multiple-reaction monitoring mode.

3.7 Blood Samples (Paper II, Study Ia)

A standard blood sample analysis was taken at HUH and analyzed at the Laboratory for Clinical Biochemistry. The blood analyses retrieved 19 different analyses consisting of essential proteins, hormones, electrolytes, and vitamins. Those were hemoglobin (Hb), erythrocyte volume fraction (EVF), mean corpuscular volume (MCV), homocysteine, transferrin receptor (TfR), thyroid stimulating hormone (TSH), free thyroxine (FT4), para-thyroid hormone (PTH), cobalamin, folate, C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (GFR), sodium, potassium, calcium, gamma-glutamyl transferase (GT), albumin, and 25 (OH) vitamin D3 (vitamin D). CRP levels lower than 1 mg/L were registered as 1 mg/L, due to limitations in the laboratory.

3.8 Questionnaires at First Evaluation (Paper I & Paper III, Study Ia & Study Ib)

The comprehensive questionnaire at the first evaluation covered pain and other symptoms, psychosocial factors, physical functioning, and traumatic events (e.g., facial trauma). The subjective experience of pain and the degree of suffering from pain in pTMD patients were assessed using a four-item General Pain Intensity Questionnaire (GPI) which utilized a Numeric Rating Scale (NRS). The patients provided self-report ratings for: (1) minimum pain intensity, (2) maximum pain intensity, (3) level of

suffering from pain, and (4) the highest pain intensity they could tolerate in their daily lives. A 0–10 NRS was used, where 0 represents no pain at all, and 10 represents the worst imaginable pain (Lundeberg et al. 2001). Other included questionnaires were the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), a two-item version of the Coping Strategies Questionnaire (CSQ) (Jensen et al. 2003) regarding pain catastrophizing, Roland Morris Scale (RMS) (Roland and Morris 1983) and a shortened version of Mandibular Function Index Questionnaire (MFIQ). The RMS consists of 24 claims regarding physical disability caused by general pain. The MFIQ is a tool for measuring mandibular function (Stegenga et al. 1993). The questionnaire utilized is a condensed version that includes five items related to mandibular function impairment regarding speech, yawning, and chewing. Work-related claims were excluded from the MFIQ in order to reduce potential bias, as a significant proportion of pTMD patients were unemployed or disabled. The claims could be ranged from 0–4, where 0 was no difficulties and 4 was impossible without help. Results from some of the HADS and CSQ were presented in Paper I (Study Ia). All questionnaires were incorporated as baseline values in Paper III (Study Ib). The healthy individuals completed the HADS and CSQ questionnaires, which were presented in Paper I.

3.9 Questionnaires at Follow-up (Paper III, Study Ib)

Three years after the multidisciplinary evaluation, the patients received a comprehensive questionnaire by mail, like the questionnaire that they filled in at the first evaluation. It included questions about the TMD and general health symptoms including MFIQ, RMS, GPI, HADS, CSQ. There were also questions regarding patients' satisfaction with the treatment conducted by their GMP. Further, there were questions regarding the development of their TMD symptoms (on a five-point scale, from much improved to much worse) and general health symptoms (on a three-point scale, from improved to worse), what kind of treatments that they had received, and the outcome of the treatments. If they did not answer the questionnaire, they were reminded by the first author via a telephone call. The results from the questionnaires at follow-up were used in

analyses in Study Ib to compare with the results from the questionnaires at first evaluation.

3.10 Neurocognitive Inhibition/ Stroop Test (Paper IV, Study II)

The neurocognitive testing of pTMD patients and healthy controls in Paper IV (Study II), was performed at the Neuropsychological Clinic at the Faculty of Psychology, University of Bergen. The applied test was the Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Functioning Scale consisting of four subtests (S) to evaluate processing speed, inhibition, and mental flexibility, (Delis et al. 2004). The CWIT is premised on the Stroop effect. The subtests include: S1) naming colours, S2) reading colours, S3) inhibition, and S4) switching. Subtest 3 comprises words that represent colours, but are printed in ink that does not match the colour of the word (e.g., the word "red" printed in blue ink instead of red ink), creating a mismatch between the word and its corresponding colour. The test subject is instructed to identify and name the colour of the ink used to print the word, rather than reading the word itself. In subtest 4, the test subject is required to switch between naming the colour and reading the name of the colour printed in a mismatching ink. A test score was recorded for each subject, reflecting the time taken in seconds to complete each subtest. Two additional CWIT measurements were calculated: 1) contrast inhibition = S3-((S1+S2)/2) and 2) contrast switching = S4-((S1+S2)/2).

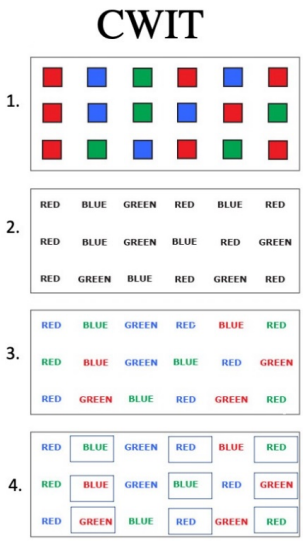

Figure 5. Presenting the four subtests (S) of the Color-Word Interference Test (CWIT): S1) naming colours, S2) reading words, S3) naming colour of the ink, not reading the word, and S4) switching between naming the colour of the ink and reading the word.

3.11 IQ Test (Paper IV, Study II)

To access the subjects´ cognitive intelligence, in order to evaluate if the cognitive inhibition test (CWIT) result were comparable between the two test groups, the Wechsler Abbreviated Scale of Intelligence (WASI) (Climie and Rostad 2011) was performed by both TMD patients and healthy controls. The included WASI was the two-subtest form, consisting of a vocabulary task and a matrix reasoning test. The test scores in numbers of correct answers were transformed into index scores based on normative tables for age and gender (Delis et al. 2001).

3.12 Questionnaires in Paper IV (Study II)

Each subject in the pTMD patient group and the control group provided personal information, including age, sex, and educational level. The study included several validated questionnaires that were self-administered by the subjects. Both the Rumination Response Scale (RRS) (Treynor et al. 2003) and the Rumination-Reflection Questionnaire (RRQ) (Trapnell and Campbell 1999) were included. The 22-item RRS is

designed to assess the extent of ruminative responses to dysphoric mood. The RRS consists of reflection, brooding, and depression-related questions, based on a yes/no scale. The RRQ is a 28-item questionnaire based on a 1-5 scale, where 1 represents 'strongly disagree' and 5 represents 'strongly agree'. The Oral Health Impact Profile (OHIP) is a reliable and validated measure of QoL related to oral health (Sierwald et al. 2011). OHIP is based on a numeric 0-4 scale, where 0 represents 'never' and 4 represents 'very often'. OHIP-TMD was the version administrated by the subjects in the present study. The OHIP-TMD is a 22-item questionnaire that has been previously reported to be a suitable psychosocial measure of QoL in patients with TMD (Yule et al. 2015). To access the subjective pain intensity and experience of pain, the subjects were asked to fill in a four-item GPI questionnaire, identical to the one in Study Ia and Ib. The Montgomery Åsberg Depression Rating Scale Self-report (MADRS-S) (Svanborg and Åsberg 2001) which is a nine-item questionnaire measuring depressive symptoms during the past three days, was also added. The MADRS-S is based on a seven-scale to evaluate the state of depression. The Perceived Deficits Questionnaire-Depression five-item (PDQ-5) (Sullivan et al. 1990) was included for a concise evaluation of self-perceived cognitive difficulties. The PDQ-5 is a five-item, five-scale (0-4) questionnaire.

3.13 Statistical Analyses

All statistical analyses were performed in STATA (StataCorp, College Station, TX, USA). STATA was continuedly updated to the newest version at the current time (starting with v.14 and ended with v. 17). Hypotheses tests were performed by a Student T-test for variables where a normal distribution was observed or reasonably expected, and by Wilcoxon (non-parametric test) for not-normal distributed variables (e.g., scores from questionnaires). The significance level was set to: alpha = 0.05. Mean, median, range, and standard deviation (SD) were calculated for continuous variables. In Study Ia, a paired T-test was performed to calculate the probability of no difference in salivary concentrations of cortisol and cortisone in Paper I, and 19 different determinants in blood in Paper II, between the pTMD-patient group and the control group. A Wilcoxon signed-

rank test was performed to calculate the probability of no difference in scores from questionnaires in Paper I and Paper II (Study Ia) and in Paper III (Study Ib) between baseline values and follow-up registrations. For further statistical analyses in Paper III (Study Ib), the patients were divided into three subgroups: 1) improvement of TMD symptoms (Gr 1), 2) no difference in TMD symptoms (Gr 2), and 3) worsening of TMD symptoms (Gr 3). A Kruskal Wallis test with a post hoc Dunn test was performed to calculate significant differences (alpha = 0.05) between the three subgroups at both baseline (first examination) and follow-up. A Wilcoxon signed-rank test was used to calculate the p-value of no difference within the three subgroups from baseline to follow-up in Paper III (Study Ib). A logistic regression model with the two subgroups Gr1 (improvement of TMD symptoms) and Gr3 (worsening of TMD symptoms) as the dependent variable and multiple independent baseline variables was performed as well. Both unadjusted model and adjusted model with stepwise forward method were calculated. For the adjusted model, the probability of enter (pe) was set to $p<0.2$, and the probability of removal (pr) was set to $p>0.4$. In Study II, mean, median, range, and standard deviation (SD) were calculated for every variable in both study groups. A p-value of no difference between the pTMD patient group and the control group was calculated by a Wilcoxon rank-sum test for all variables.

4. Main Results

4.1 Demographic Data of the First 60 TMD Patients (Paper I, Paper II & Paper III, Study Ia & Study Ib)

The group of the first 60 TMD patients, multidisciplinary evaluated at HUH, consisted of 51women and nine men, all affected with severe TMD symptoms. Mean pain duration in the patient group was 11 years (ranged 1-40). Mean age of the patient group was 45 years (ranged 20-69). Registered main diagnoses on our clinical examination of the TMD group were myalgia (n=22), arthralgia (n=1), disc derangement (n=1), and combinations thereof (n=35). Additional comorbid diagnoses comprised fibromyalgia (n=8), migraine (n=12) and chronic fatigue (n=4). Regular medications used by the patients were paracetamol (n = 28), NSAIDs (n = 23, hereunder celecoxib in one patient), opioids (n = 20, hereunder strong opioids in five patients and weak opioids in 17 patients), antidepressants (n = 15, hereunder tricyclic antidepressants in seven patients and selective antidepressants in 10 patients), zopiclone (n = 7), clonazepam (n = 3), gabapentinoids (n = 6, hereunder gabapentin in four patients and pregabalin in two patients), carbamazepine (n = 1), and topiramate (n = 1).

4.2 Paper I (Study Ia)

4.2.1 Demographic Data Paper I

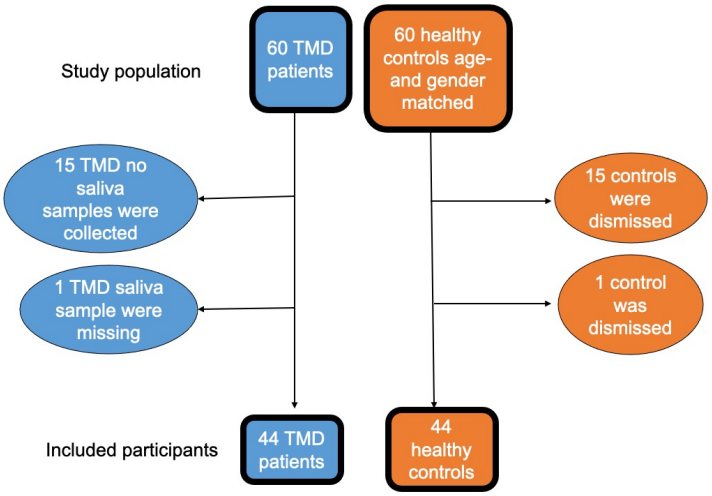

Figure 6. The multidisciplinary evaluation programme for TMD patients at Haukeland University Hospital consisted of 60 pTMD patients, all affected with long-term refractory TMD symptoms, and 60 healthy age- and sex-matched control subjects. Because no saliva sampling was done for the first 15 pTMD patients and one saliva sample was missing from the patient group, the population in the present study ended up with 44 pTMD patients and 44 healthy controls. The patients were aged 20-69 years, with a mean age of 44 years. The control subjects were aged 23-71 years with a mean age of 46 years. Both groups consisted of 38 women and six men.

4.2.2 Saliva Samples

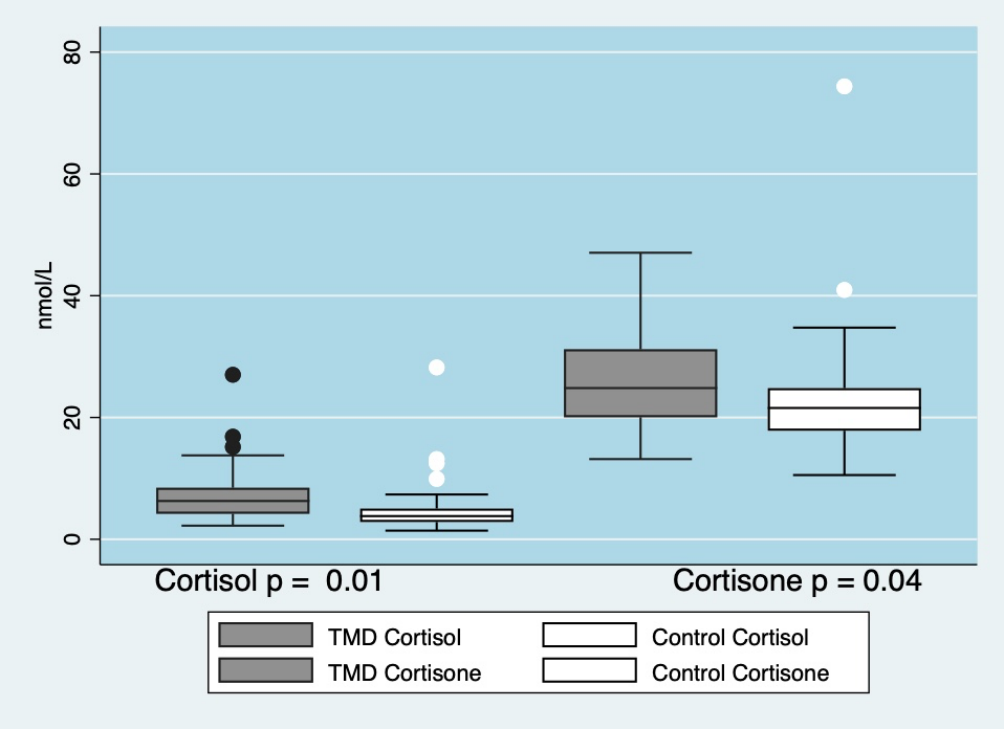

Figure 7. A paired T-test revealed that concentrations of salivary cortisol and cortisone, determined by liquid chromatography–tandem mass spectrometry (LC-MS/MS), was significantly higher in pTMD-patients compared to healthy individuals.

The pTMD patient group had a mean saliva sampling time point of 2 h, 52 min. after awakening. The saliva samples were mostly collected at 9:00 a.m. but a few were collected at 11:00 a.m. due to logistical factors. All subjects in the control group collected saliva 2 h, 45 min. after awakening, matching the mean sampling time of the TMD patient group. Saliva samples from the control group were collected between 8:00 a.m. and 10:00 a.m. The transitions monitored under LC-MS/MS analyses were 407.24→331.26 for cortisol and 405.22→329.24 for cortisone. The linearity range was 0.3–50 nmol/L for cortisol and 0.7–100 nmol/L for cortisone. Accuracy was between 87% and 110%, and total imprecision was <10%.

4.2.3 Psychosocial Questionnaires Paper I

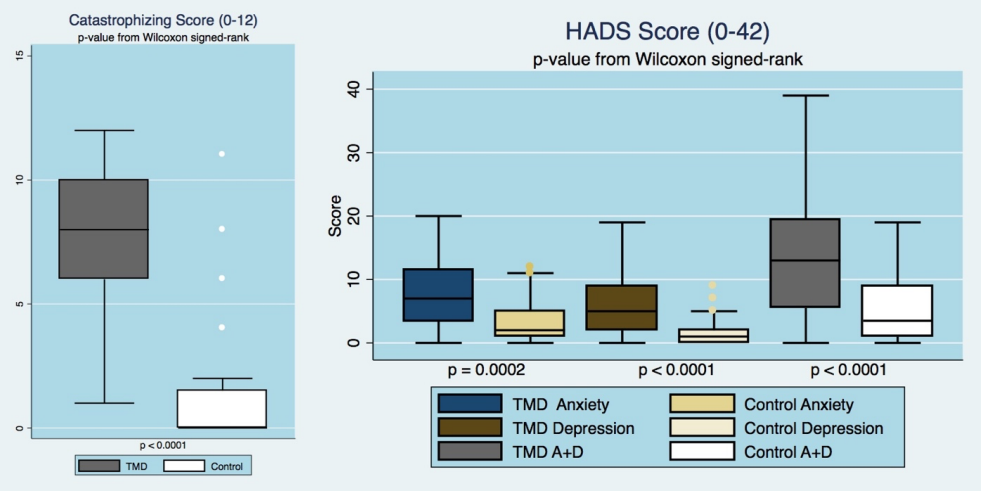

Figure 8A-8B; A Wilcoxon signed-rank test revealed significantly higher scores from the psychosocial related questionnaires in pTMD patients compared to healthy controls. The included questionnaires were the Coping Strategies Questionnaire (CSQ) (Fig 7A), and the Hospital Anxiety Depression Scale (HADS), consisting of two subscales: Anxiety (A) and Depression (D) (Fig 7B).

4.3 Paper II (Study Ia)

4.3.1 Demographic Data Paper II

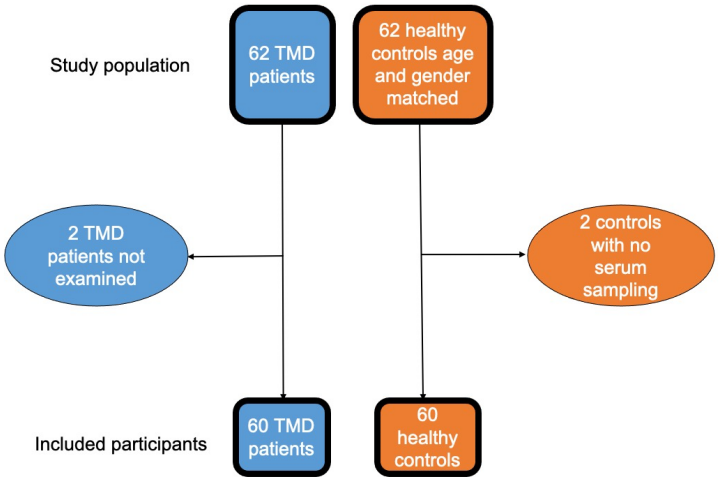

Figure 9. Study II included all 60 TMD patients and 60 healthy controls from the multidisciplinary evaluation programme at HUS. The control group was matched for age and gender and had a mean age of 46 years (ranged 23-71).

4.3.2 Blood Samples

A paired T-test revealed that pTMD patients had significantly higher concentrations of hemoglobin (Hb) ($p=0.036$), cobalamin ($p=0.023$), albumin ($p=0.005$), parathyroid hormone (PTH) ($p=0.038$), and vitamin D ($p=0.005$), but significantly lower concentrations of creatinine ($p=0.006$) and potassium ($p=0.011$) in blood compared to controls. No differences were observed in blood concentrations of erythrocyte volume fraction (EVF), mean corpuscular volume (MCV), homocysteine, transferrin receptor (TfR), thyroid stimulating hormone (TSH), free thyroxine (FT4), cobalamin, folate, C-reactive protein (CRP), estimated glomerular filtration rate (GFR), sodium, calcium, or gamma-glutamyl transferase (GT) between TMD patients and controls.

On the individual level, the majority of all blood analyses in both pTMD patients and healthy controls were within normal ranges. Some minor exceptions were observed. Mild to moderate vitamin D level deficiency was observed in 11 pTMD patients, compared to 18 controls. Furthermore, we observed marginally elevated levels of CRP (n=7), and elevated levels of transferrin receptor (n=7) and homocysteine (n=6), as well as lowered levels of erythrocyte volume fraction (EVF) (n=5), in the TMD group. FT4 was elevated in three patients and lowered in one patient, while parathyroid hormone (PTH) was elevated in two patients and lowered in four patients. Concentrations of calcium and creatinine in blood were normal in patients who used celecoxib, pregabalin, and topiramate and were within normal reference values. One patient who used carbamazepine had slightly elevated concentration of serum TfR (5.7 mg/L) and normal concentration of Hb.

4.4 Paper III (Study Ib)

4.4.1 Demographic Data Paper III

Of the 60 pTMD patients who participated in the multidisciplinary evaluation programme, 39 patients answered the received questionnaires at the three-year follow-up. The baseline characteristics of responders and non-responders are presented in Table 2.

Three-year follow-up	All patients at baseline	Responders three-year follow-up	Non-responders three-year follow-up
n patients	60	39	21
Baseline values			
Sex ratio F:M	6:1	9:1	3:1*
Age years: mean (range)	45 (20–69)	47 (24–69)	40 (20–69)*
Pain duration in years: mean (range)	11(1–40)	13 (1–40)	7 (2–18)*
Psychosocial measures:			
HADS: mean (range)	13.1 (0–39)	12.3 (0–39)	14.7 (1–38)
CSQ: mean (range)	7.1 (2–12)	7.4 (2–12)	7.0 (1–12)
GPI maximum: mean(range)	8.6 (4–10)	8.9 (6–10)	7.6 (0–10)
GPI suffering: mean(range)	7.9 (2–10)	8.0 (6–10)	7.3 (0–10)

Table 2. Responders at the follow-up (n = 39) had significantly (*) higher age, longer pain duration, and a higher female representation compared to non-responders (n=21). No differences were observed in scores from psychosocial related questionnaires, including Coping Strategies Questionnaire (CSQ), General Pain Intensity Questionnaire (GPI), or Hospital Anxiety Depression Scale (HADS) in responders compared to non-responders.

4.4.2 Self-reported Health and TMD Symptoms Paper III

TMD symptoms were reported improved in 10 out of 39 patients (26%), unchanged in 16 patients (41%), and worsened in 13 patients (33%), at the three-year follow-up. General health was reported improved in six patients (15%), unchanged in 17 patients (44%) and worsened in 12 patients (31%). Only eight patients (21%) were satisfied with the follow-up by their GMP, while 15 patients (39%) were dissatisfied. Eleven patients (28%) were not sure, and three patients (8%) reported that their GMP did not follow up the suggested treatments from the multidisciplinary team at all. Two patients (5%) did not answer.

4.4.3 General Pain Intensity on a NRS Scale (0-10) Paper III

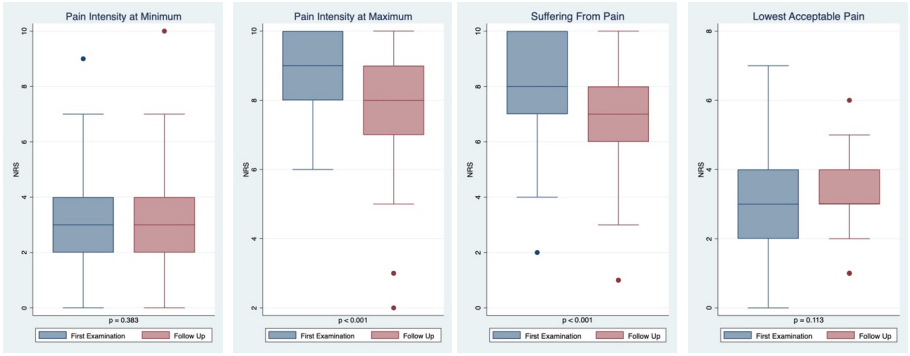

Figure 10A-10D. Improvements in the maximum pain intensity (NRS 0-10) were reported at the three-year follow-up (decrease in median from NRS 9.0 to 8.0; $p<0.001$), and the highest level of suffering from pain decreased (decrease in median value from NRS 8.0 to 7.0; $p<0.001$). No statistical differences were reported in the minimum pain ($p=0.38$), or in the option of the highest pain intensity that the patients would accept to live with ($p=0.11$).

4.4.4 Psychosocial and Functional Related Questionnaires Paper III (Study Ib)

Score from questionnaires	HADS (0–42)	CSQ (0–12)	RMS (0–24)	MFIQ (0–24)
Baseline (First examination)				
Median	11.0	8.0	7.0	12.0
Range	0.0–39.0	2.0–12.0	1.0–21.0	2.0–22.0
Follow-up				
Median	11.0	6.5	6.0	10
Range	0.0–38.0	0.0–12.0	0.0–21.0	0.0–20.0
n patients	38	38	37	38
p-value (Wilcoxon signed-rank)	0.175	0.033	0.218	<0.001

Table 3. A Wilcoxon signed-rank test was performed to calculate the probability of no difference between the baseline values and the three-year follow-up. The results from the Coping Strategies Questionnaire (CSQ) showed a significantly lower score at the follow-up (decrease in median value from 8.0 to 6.5; p=0.03), and in the Mandibular Function Index Questionnaire (MFIQ) (decrease in median value from 12.0 to 10.0; p<0.001). No statistical differences were observed in the Hospital Anxiety Depression Scale (HADS) (p=0.175), or in the Roland Morris Scale (RMS) (p=0.218). The majority of the questionnaires were completed by 38 out of 39 patients at both the initial examination and the follow-up, with the exception of RMS, which was completed by 37 out of 39 patients.

4.4.5 Subgroup Analysis Paper III (Study Ib)

The three subgroups in Paper III included patients with improvement of TMD symptoms (Gr 1, 10 patients), no difference in TMD symptoms (Gr 2, 16 patients), and worsening of TMD symptoms (Gr 3, 13 patients). In the group that reported worsening of TMD symptoms (Gr 3), the maximum pain intensity was significant higher at baseline compared to the two other groups. Gr 3 had also a significant higher minimum pain intensity, higher maximum pain intensity, and higher level of suffering from pain at the follow-up, followed by Gr2>Gr1. Further, Gr 1 showed significantly lower minimum pain, maximum pain, and suffering from pain at the follow-up.

No statistical differences were seen between the three subgroups at baseline analyzing HADS, CSQ, RMS, and MFIQ. But at the follow-up, significantly lower (positive outcome) CSQ score in Gr 1, and significantly higher (negative outcome) MFIQ in Gr 3 were seen. Improvement in MFIQ scores was observed within Gr 1 and Gr 2 from baseline to the follow-up, while only the patients in Gr 1 had a significant decrease in CSQ score from baseline to follow-up.

Dependent variable: TMD symptoms at follow-up: worse (Gr3, n=13) vs improved (Gr1 n=10)			
Logistic regression: Unadjusted model			
Independent baseline variable	**Description**		**p:**
Age	Age in years at baseline		0.53
Gender	Gender: female/ male		0.42
HADS Score	Hospital Anxiety Depression Scale score at baseline		0.57
CSQ Score	Coping Strategies Questionnaire score at baseline		0.32
RMS Score	Roland Morris Scale score at baseline		0.20
MFIQ Score	Mandibular Function Index Questionnaire score at baseline (work excluded)		0.28
GPI Minimum	General Pain Intensity on a Numeric Rating Scale (0–10) at baseline: when at minimum		0.56
GPI Maximum	General Pain Intensity on a Numeric Rating Scale (0–10) at baseline: Pain intensity when at maximum		0.02
GPI Acceptable	General Pain Intensity on a Numeric Rating Scale (0–10) at baseline: Lowest pain intensity to accept to live with		0.14
GPI Suffering	General Pain Intensity on a Numeric Rating Scale (0–10) baseline: Suffering from pain		0.14
Multivariable logistic regression: Adjusted stepwise, forward			
Worse/Improved	**OR**	**p**	**95% CI**
GPI Maximum	5.79	0.018	1.34 24.96

Table 4. A logistic regression model with the two subgroups Gr1 and Gr3 as the dependent variable and multiple independent baseline variables. Both unadjusted model, and adjusted model with stepwise forward method were performed. At baseline, pain intensity at maximum was the only variable to be significantly associated with worsening of TMD symptoms at the follow-up.

4.5 Paper IV (Study II)

4.5.1 Demographic Data Paper IV

Out of a total of 129 patients with pTMD from the National pTMD project at HUH, 126 received an invitation to participate in the study. Among them, 39 patients signed up to participate, and 22 of them completed the tests in the present study. In the control group, 11 out of 19 subjects were randomly selected from the Norwegian National Population Register, while the remaining control subjects were recruited from acquaintances and co-workers at the university who were not part of the research group in the present study. The final study group comprised of 20 women and 2 men in the pTMD group, and 17 women and 2 men in the control group. Further details of the study population are presented in Figure 10.

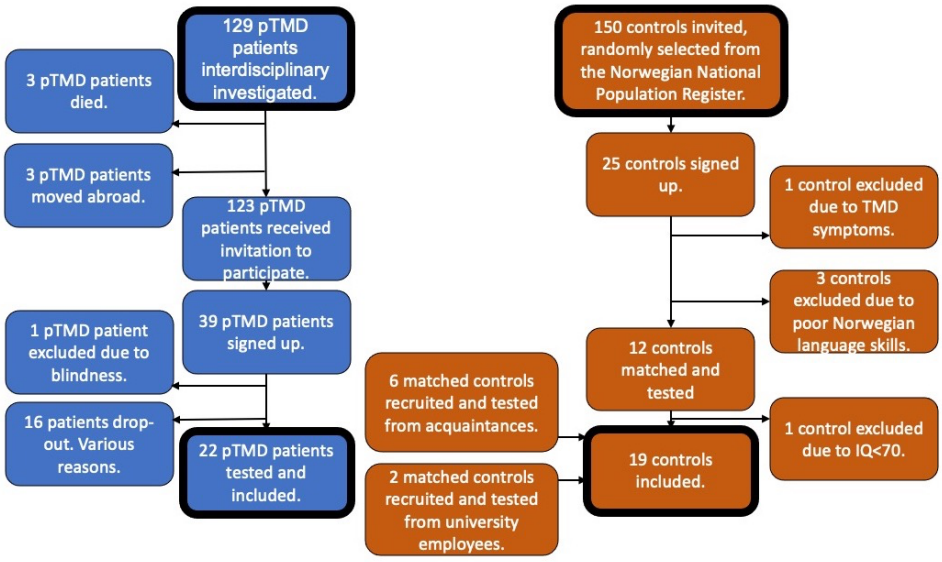

Figure 11. Included pTMD patients and controls in Paper IV.

There were no statistical differences in age, educational level, and IQ between the pTMD group and the control group. The TMD diagnoses in the group of 22 pTMD patients

were myalgia (n = 10), arthralgia (n = 2), disc derangement (n = 3), and combinations (n = 7).

4.5.2 Neurocognitive Inhibition (Paper IV, Study II)

There were no statistical differences on CWIT performance, hereunder S1 colour naming, S2 reading, S3 inhibition, S4 switching, contrast inhibition, and contrast switching, between the pTMD group and the control group (Table 5).

Stroop time	**S1 Naming colours** (Sec)	**S2 Reading** (Sec)	**S3 Inhibition** (Sec)	**S4 Switching** (Sec)	**Contrast inhibition** S3-((S1+S2)/2)	**Contrast switching** S4-((S1+S2)/2)
TMD						
(n=22; 20W, 2M)						
Mean	34.7	25.9	67.3	82.7	37.0	52.4
Median	33.0	24.0	58.5	72.0	29.8	39.0
Range	24-60	16.0-55.0	39.0-187.0	46.0-276.0	14.5-129.5	21.5-218.5
SD	10.0	8.4	30.5	47.8	23.7	41.5
Control						
(n=19; 17W, 2M)						
Mean	33.5	24.4	56.6	72.6	27.6	43.6
Median	34.0	24.0	55.0	71.0	27.5	42.0
Range	21.0-48.0	18.0-39.0	44.0-87.0	54.0-111.0	18.5-49.5	25.0-79.0
SD	7.6	5.3	9.6	15.8	7.1	13.4
***p*-value** (Wilcoxon exact)	1.000	0.790	0.200	0.964	0.113	0.974

Table 5. Test results from CWIT. Times to complete each subtest in both study groups are presented in seconds.

4.5.3 Questionnaires (Paper IV, Study II)

Rumination scores from the RRQ questions 1-12, and the RRS, were significantly higher in the pTMD group. Depression scores from the MADRS were also significantly higher in the pTMD group. Self-perceived cognitive function, shown by the PDQ, was significantly poorer in the pTMD group. The score from the OHIP-TMD revealed there was a significantly poorer QoL related to oral health in the pTMD group. There were no differences in reflection scores from the RRQ questions 13-22. Details of results from the questionnaires are presented in Table 6.

Questionnaires	**RRQ 1-12** (Score 12-60)	**RRQ 13-24** (Score 12-60)	**RRS** (Score 22-88)	**MADRS** (Score 0-54)	**PDQ** (Score 5-20)	**OHIP TMD** (Score 0-88)
TMD						
(n=22; 20W, 2M)						
Mean	35.3	35.8	35.6	9.7	12.5	43.9
Median	36.0	35.0	33.5	8.0	12.0	43.0
Range	20-48	27-57	23-50	2-27	8-19	17-67
SD	7.5	7.2	8.0	6.1	2.9	13.5
Control						
(n=19; 17W, 2M)						
Mean	27.1	33.7	30.4	4.0	8.5	5.2
Median	27.0	32.0	27.0	3.0	9.0	1.0
Range	12-43	22-45	22-53	0-15	5-15	0-36
SD	8.5	7.1	8.9	3.9	2.5	9.0
***p*-value** (Wilcoxon exact)	0.003	0.564	0.021	<0.001	<0.001	<0.001

Table 6. Results from the questionnaires in Paper IV. All scores were significantly higher in the pTMD group, except the reflective rumination score.

5. Discussion

In the group of pTMD patients from the present study, we suspected psychosocial stress as an important characteristic. In Paper I, the pTMD patients had significantly elevated scores in psychosocial-related questionnaires, including the HADS and the CSQ, compared to a healthy control group. As a biologic marker of stress, we observed cortisol concentration in saliva to be significantly higher in pTMD patients compared to the control group in Paper I. Also, in Paper III, we observed that significantly lowered CSQ score at the three-year follow-up was associated with improvement of TMD symptoms. In another study of the same pTMD population (Study I), it was observed that CSQ score was more strongly associated with the patient group than any other variable, including other psychosocial, functional, and experimental pain variables (Willassen et al. 2020). In a study of the pTMD population in Study II, higher catastrophizing was associated with higher psychosocial distress (Anker et al. 2023). In a study of 163 TMD patients, pain-related catastrophizing and depression were observed to be the most significant factors in pain persistence (Reiter et al. 2018). Similarly, psychosocial stress shown by elevated CSQ score has been reported as a major risk factor in development of general chronic pain, and also as an predictor of poorer prognosis in pain relief (Landmark et al. 2018). Previous reports from a large longitudinal study in the US, the OPPERA study, also identified psychosocial stress, including anxiety, depression, and pain-related catastrophizing, as important characteristics of TMD (Fillingim et al. 2011; Fillingim et al. 2018; Slade et al. 2016). The complex involvement of stress in TMD is thought to affect biological systems including neuroendocrine function and pain perception, and also psychosocial and physical adjustments (Gameiro et al. 2006).

Stress activates the HPA axis, leading to enhanced secretion of cortisol, which in turn leads to several physiologic responses (Smith and Vale 2006). It has also been discussed that the stress response in chronic pain conditions may lead to a dysregulation of the HPA axis (Woda et al. 2016). In Paper I, we observed that a

liquid chromatography–tandem mass spectrometry (LC-MS/MS) analysis of saliva revealed that pTMD patients had significantly higher concentrations of cortisol and cortisone compared to a healthy control group. Several previous studies have also shown higher levels of cortisol in TMD patients compared to healthy individuals (Chinthakanan et al. 2018; Da Silva Andrade et al. 2008; Korszun et al. 2002; Salameh et al. 2015). A significantly higher cortisol concentration as a response to experimental stress in subjects with TMD has also been reported (Jones et al. 1997). However, all those studies were obtained with immune assays, which are well known to have a lower specificity for cortisol compared to LC-MS/MS (Miller et al. 2013). Cortisol concentration in healthy individuals also follows circadian fluctuations, with a peak curve approximately 30-45min after awakening; as a consequence, accurate sampling time is important for the results (Smyth et al. 2013; Wilhelm et al. 2007).

Paper III was a three-year follow-up study, which investigated the TMD patients' subjective report of their symptoms. Three years after the multidisciplinary evaluation programme for TMD patients at HUH in Norway, only one-third of the patients reported improvement of TMD symptoms, and one-third reported worsening of TMD symptoms. We observed that the subgroup of patients who reported improvement of TMD symptoms reported significantly lower pain intensity at baseline compared to the subgroup which reported no difference, and the subgroup which reported worsening of TMD symptoms. The subgroup which reported improved TMD symptoms also reported significantly lower pain intensity, significantly improved mandibular function as shown by the MFIQ and, as previously discussed, significantly lower CSQ score at the follow-up compared to baseline. To consider the whole group of TMD patients at the follow-up, the pain intensity at the highest level and how much the patients suffer from pain had significantly decreased from baseline. However, the pain intensity was still considerably high. Higher pain intensity has also been associated with poorer TMD prognosis in a previous longitudinal study (Forssell et al. 2017). Another study showed that patients who experience pain more frequently have a poorer prognosis of TMD recovery (Rammelsberg et al. 2003). Long-term follow-up from the OPPERA study has shown

that adaption to chronic pain might result in decrease of pain intensity over time (Fillingim et al. 2018). In a large longitudinal study, longer duration of pain and higher pain intensity were significantly associated with reinforced anxiety and depression disorders (Gerrits et al. 2012). Psychosocial factors are considered important in perception and tolerance of pain (Bélanger et al. 2017). The experience of fear related to pain is individual and may increase pain intensity and anxiety in a two-way system (Ochsner et al. 2006), where pain leads to avoidance of physical activity and the anxiety related to pain might increase the focus on pain and result in higher suffering (Vlaeyen and Linton 2000). Chronic pain and psychological symptoms such as anxiety and depression are commonly observed together and may reinforce each other. This will impair the prognosis for recovery from chronic pain (Gerrits et al. 2012; Stevans et al. 2021).

There is evidence that chronic pain patients should be investigated in a multidisciplinary manner so as to improve their quality of life (Ahmed et al. 2014). They should also be treated with a multidisciplinary approach, as it is important to manage psychological and physiological comorbidities simultaneously, to achieve the intended treatment outcome in patients with chronic orofacial pain (Zakrzewska 2013). In our study, the TMD patients were investigated by the multidisciplinary team at HUH, where an individual treatment plan was developed for each patient. The treatment plan was presented to the patients and was supposed to be followed up by their GMP. Three years after the multidisciplinary evaluation at HUH, only eight out of 39 pTMD patients were satisfied with the follow-up from their GMP. It is possible that the treatment outcome would be further improved if the patients were more satisfied with the follow-up by their GMP, and if the treatment plan from the multidisciplinary team was followed accurately. However, most of the patients resided in other parts of the country than where they were investigated, and were referred back to be treated at their place of residence. Since specialists are concentrated in cities in Norway, there can be lack of specialist treatments and multidisciplinary teams in rural areas. This might explain why most patients did not get the opportunity to be treated in a multidisciplinary way. Other factors that may explain why most patients in the present study did not report improvement in TMD

symptoms might possibly be due to the patient group with long-term refractory pain. Treatment of long-term chronic pain, especially in combination with psychosocial factors, has a poor prognosis according to a large longitudinal pain study in Norway (HUNT Study) (Landmark et al. 2018). To have several TMD-associated clinical findings has also been associated with a poorer treatment outcome compared to if there is only one (Sanders et al. 2016).

In Paper IV, the group of pTMD patients reported higher pain intensity, more self-perceived neurocognitive difficulties, low oral health-related quality of life (QoL), and higher levels of rumination and depression compared to a control group. However, there were no significant differences in neurocognitive inhibition measured by a Stroop test, in this case the CWIT, between the pTMD group and the control group.

A previous study of 17 TMD patients observed a slower response to Stroop tasks compared to a control group (Weissman-Fogel et al. 2011). There are few studies of cognitive inhibition in groups of TMD patients. However, several studies on patients with fibromyalgia and general chronic pain have explored the association between chronic pain and impaired cognitive function. In line with our results, a study of fibromyalgia patients reported subjective complaints from patients, while cognitive inhibition assessed with a Stroop task did not differ significantly from a healthy control group (Veldhuijzen et al. 2012). Another study of patients with fibromyalgia showed poorer attention; however, executive function, and hereunder inhibition, did not differ from the control group (Oosterman et al. 2012). On the other hand, findings from other studies using a Stroop test, have demonstrated slower cognitive processing in patients with fibromyalgia compared to healthy individuals (Martinsen et al. 2014). Better cognitive inhibition, as measured by Stroop interference score, has also been associated with lower pain intensity in healthy individuals. (Oosterman et al. 2010). Similarly, patients with high intensity chronic pain have shown to exhibit poorer cognitive inhibition compared to healthy individuals (Grisart and Plaghki 1999). A meta-analytic review reported that there is a small to medium evidence of impaired cognitive function in populations with chronic pain, although findings are

contraindicatory (Berryman et al. 2014). In the present study, the lack of significant differences in cognitive inhibition between the pTMD group and the control group may be attributed to the small sample size or potential selection bias, as the recruitment rate for participation in the study was low.

The group of pTMD patients in Paper IV reported significantly higher self-perceived neurocognitive deficits shown by PDQ, and reduced QoL compared to the healthy controls. The finding that neurocognitive inhibition, as measured by the CWIT, did not differ significantly between the pTMD group and the control group suggests that the ability to manage chronic pain and perform everyday tasks may be more closely related to self-perceived cognitive deficits rather than executive function. One previous study has also demonstrated that patients with chronic idiopathic pain exhibit self-perceived cognitive deficits as measured by the PDQ, along with increased pain-related disability and reduced quality of life, when compared to a healthy control group. (Coppieters et al. 2017). It seems that patients with chronic pain and pain-related disabilities may experience self-perceived cognitive deficits and depression, even when their executive function is within the expected range observed in healthy individuals.

In Paper IV, the group of pTMD patients reported significantly higher levels of depressive rumination (RRS) and neurotic rumination (RRQ question 13-24). However, reflection (RRQ question 1-12), which is considered as an adaptive form of rumination, did not differ from the control group. Rumination may also exacerbate pain (Meints et al. 2017), disrupt cognitive functioning, and contribute to depression, anxiety, and insomnia (Watkins and Roberts 2020), and lead to relapse and recurrence of depression (Ronold et al. 2020a). Neurotic rumination has been associated with a more severe course of illness in depression, and has shown to influence sensitivity to negative emotions, (Ronold et al. 2020b). Thus, the relatively high levels of depression in the pTMD group may be attributed, in part, to the presence of neurotic rumination. Importantly, there were no significant differences in reflection between the pTMD group and the control group, suggesting that it was more pathological emotion regulation mechanisms that were heightened in this group.

Results from the OHIP-TMD questionnaire in Paper IV showed that the pTMD group had significantly poorer oral health-related QoL compared to the control group. A previous study has also found a correlation between poorer oral health-related QoL and increased severity of TMD (Yap et al. 2022). In another study, TMD patients exhibited significantly lower oral health-related QoL compared to a control group, and oral health-related QoL was also significantly correlated with higher pain intensity in the TMD group (Onoda et al. 2021). Altogether, findings indicate that the severity and pain intensity in TMD are significantly associated with subjective cognitive deficits and poorer QoL.

The blood samples in Paper II revealed that most of the pTMD patients and healthy controls had concentrations within the normal biologic range of nineteen common diagnostic analyses, including essential proteins, hormones, ions, and vitamins. However, we observed that p TMD patients had significantly higher values of hemoglobin, cobalamin, albumin, parathyroid hormone (PTH), and vitamin D, and significantly lower values of creatinine and potassium, compared to the control group. An unexpected result revealed that the control group had significantly lower values of vitamin D compared to the TMD group. In both groups, a mild deficiency in vitamin D was commonly observed. Supporting observations have also been reported from one study regarding current high prevalence of vitamin D deficiencies in both TMD patients and healthy controls (Demir and Ersoz 2019). Elevated levels of PTH in TMD patients compared to healthy controls have also previously been reported (Demir and Ersoz 2018). Contraindicatory to the present study, a high prevalence of malnutrition, including deficiencies in vitamin D, vitamin B, and iron, were observed in a population of TMD patients (Ahmed S 2016), as well as a high prevalence of low serum vitamin B, folate, and iron (Mehra and Wolford 2008).

The present thesis has some limitations. Some of the applied questionnaires that were validated in their original language were not validated in the version translated to Norwegian. However, the Norwegian Institute of Public Health (FHI) has evaluated the Norwegian version of the HADS questionnaire to be a fairly validated tool of measuring psychologic distress (Leiknes et al. 2016). The reliability and validity of

the self-reported questionnaires is also a limitation. A previous study examining treatment outcomes for TMD reported a significant discrepancy of 44% between the evaluations made by doctors and the self-reported answers provided by patients on a TMJ symptom and function assessment questionnaire. (Ness and Laskin 2012). Our study had a relatively small population. The control group in Paper I and Paper II consisted mainly of employees and some students from the Department of Clinical Dentistry at the University of Bergen, and they were not socioeconomically matched with the TMD patient group. A limitation in Study Ia was that the blood samples were taken at all seasons of the year, while the concentration of some determinants, e.g., vitamin D and PTH, may have some seasonal variability in the northern countries. The response rate in Paper III, and the fact that the patients were not clinically examined at follow-up, should also be considered as a limitation. We had no control over whether the patients, with follow-up from their GMP, followed the suggested treatment plan from the multidisciplinary team at HUS. The subgroups in Paper III were also very small, which resulted in a broad confidence interval in the regression analysis and thus the validity of results might be questionable. However, statistical analyses are adjusted for population size, and the study shows important results of a patient group that is demanding to recruit and to investigate. The limitations of Paper IV were the small sample size and possibly selection bias. The recruitment rate was low in both the pTMD group and the control group, and it is possible that individuals with poor cognitive skills may have chosen to avoid participating in the study due to concerns about their performance in cognitive tasks.

Altogether, we observed some potentially important characteristics in our group of pTMD patients, including higher psychosocial stress, catastrophizing, self-perceived cognitive deficits, rumination, depression, and low QoL related to oral health. High pain intensity was considered as a risk factor for poorer recovery. On the other hand, neurocognitive inhibition and biomarkers in blood did not differ significantly from healthy individuals.

6. Conclusion

As a general conclusion, the pTMD patients in our study suffered from high levels of psychosocial stress, including self-perceived cognitive deficits, anxiety, depression, rumination, pain-related catastrophizing, and low QoL related to oral health. All the above factors might be important characteristics of pTMD. These factors may make it more difficult to master chronic pain and common everyday tasks, suggesting that they could be targeted in treatment and interventions. Professional health treatment and management of pTMD may be improved by personalized programmes, pain mastering courses, and cognitive training. However, the tested neurocognitive performance in the patient group was equivalent to the control group.

All of the he pTMD patients suffered from high pain intensity (> NRS 6). Higher pain intensity in patients with pTMD was significantly associated with poorer recovery, three years after a multidisciplinary evaluation and treatment suggestion. The results indicate that patients with extremely high pain intensity might be at risk of non-resolving TMD. Improved coping with TMD pain included both decreased pain intensity and pain-related catastrophizing scores.

The pTMD patients had significantly higher concentration of salivary cortisol and higher psychosocial stress shown by scores from questionnaires compared to a healthy control group. These results indicate that pTMD patients may have an upregulated HPA axis. The majority of the pTMD patients had blood concentrations of essential proteins, hormones, ions, and vitamins within normal biologic range. We were unable to associate any severe systemic disease, malnutrition, or systemic inflammation with pTMD, and therefore we would not recommend blood samples for screening of pTMD patients.

7. Future Perspectives

7.1 Research Perspectives

In future follow-up studies of pTMD patients, it would be preferable to follow the patients after the multidisciplinary evaluation, to see if the recommended treatment plan is applied and followed up by the GMP, and how outcome of recommended treatments affects the patients' subjective TMD symptoms.

In future cortisol studies of pTMD patients, it would be interesting to collect samples at several time points to investigate the diurnal rhythm of cortisol. The measure of cortisol response to experimental stress would also be expedient. In neurocognitive testing, it would be interesting to perform a fMRI brain scan while performing a Stroop task, and also to recruit a larger study population.

New clinical perspectives should also be incorporated in longitudinal studies, which could show treatment outcomes of the new interventions.

7.2 Clinical Perspectives

The future goal of management of TMD patients must be to prevent chronic pain and disability. Suggestions to achieve this might be through an individualized and tailored pain management programme for each patient, including both medical and psychosocial domains. A 'learning and mastering' course has already been established for TMD patients at HUS and is hopefully going to improve the patients´ ability to cope with pain and their QoL. A digital treatment course is previously established which functions in the gap between the interdisciplinary examination and start of treatments back home, where the patients have been referred for treatment. A personalized, digital rehabilitation programme with feedback is planned to be established, and which may give the patients the opportunity to take responsibility for their own recovery and improve the outcome of treatment. The digital intervention will increase the access to secure and effective training that can improve patients'

health by providing online self-help programmes with information and exercises presented as text, audio, and video, including monitoring of symptoms and progress. There is also a need for education of healthcare professional in management of TMD, and to establish specific positions for orofacial pain specialists.

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Research Article

Temporomandibular Disorders Related to Stress and HPA-Axis Regulation

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Temporomandibular disorders (TMDs) are characterized by pain and dysfunction in the masticatory apparatus and the temporomandibular joint (TMJ). Previous trauma, stress symptoms, psychosocial impairment, and catastrophizing have been related to TMD. To assess if the hypothalamic-pituitary-adrenal (HPA) axis is upregulated in TMD patients, we performed a cross-sectional study with saliva from 44 TMD patients and 44 healthy sex- and age-matched controls for cortisol (F) and cortisone (E) with liquid chromatography-tandem mass spectrometry. Furthermore, we calculated the F/E ratio for the evaluation of 11β-hydroxysteroid dehydrogenase activity. We also assessed anxiety/depression and pain catastrophizing scores from a questionnaire that participants completed prior to the examination. We found that F ($P = 0.01$), E ($P = 0.04$), the F/E ratio ($P = 0.002$), and the sum of glucocorticoids ($E + E$) in saliva ($P = 0.02$) were significantly higher in the TMD group. Anxiety/depression and catastrophizing scores were also significantly higher in the TMD group ($P < 0.0001$). Our findings indicate that patients with TMDs may have an upregulated HPA axis with higher F secretion from the adrenal cortex. Anxiety/depression and pain catastrophizing scores were significantly higher in the TMD group, and psychological factors may contribute to chronic upregulation of the HPA axis.

1. Introduction

Temporomandibular disorders (TMDs) are a group of disorders associated with pain and dysfunction affecting the temporomandibular joint (TMJ) and the masticatory apparatus [1, 2]. TMDs occur predominantly in women, who are especially likely to experience more severe symptoms. TMD-associated comorbidities include fibromyalgia, irritable bowel syndrome, and depression, with trauma and stress symptoms frequently present as well [3]. Psychosocial impairment within a TMD, such as somatization and depression, is linked with pain-related disability as well as the duration of pain [4]. The Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study found that psychosocial factors (e.g., somatic awareness, distress, catastrophizing, pain amplification, and psychosocial stress) had a significantly higher prevalence in subjects with a TMD compared to healthy individuals [2, 5].

During the last few decades, use of physiological markers for assessing psychosocial-related disorders has increased. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which results in a cascade of reactions leading to increased secretion of cortisol from the adrenal cortex. Research examining the HPA axis response to stress has yielded contradictory results. A meta-analysis of chronic stress and HPA-axis activity found that HPA response to stress varies with the nature and controllability of stressful stimuli as well as the individual psychiatric response [6]. The role of stress in the etiology and persistence of TMD remains unclear. However, dysregulation of the HPA axis has been correlated with TMD in several studies [7–9]. Accordingly, analysis of

cortisol (F) levels in saliva may provide a means for examining HPA-axis activity.

Salivary F levels follow circadian fluctuations, and these variations can be used to create a curve depicting unbound free and total cortisol in serum [10]. However, previous analyses of F in saliva from TMD patients have given variable results. Some researchers have found elevated F values in association with TMD [11, 12], while others have not found any significant difference in comparison to a control group [13]. Analyses using immunoassay methods [11–15] have also been undertaken to measure F in saliva from subjects with a TMD. These methods do not separate cortisol (F) and cortisone (E), which have structural similarities but unequal biological activities. Recent F and E analyses based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) are now available [16].

The primary objective of this study was to assess the stress levels in TMD patients based on an upregulated HPA axis and compare the results with healthy individuals. Secondary objectives were to analyze the saliva for F and E and the scores for self-reported anxiety/depression and catastrophizing from a questionnaire. The hypothesis was that TMD patients have an upregulated HPA axis shown by increased psychological scores and increased level of cortisol in saliva.

2. Materials and Methods

2.1. Study Design. The present study is a clinical cross-sectional study, which was a part of a multidisciplinary investigation of TMD patients at Haukeland University Hospital, sponsored by the Norwegian Ministry of Health [17]. Ethical approval was granted by the Regional Ethical Review Board South East (2015/930), in accordance with the Helsinki Declaration (1964). A written informed consent was received from all subjects.

2.2. Participants. All TMD patients ($n = 60$) were referred by their general practitioner to the National TMD project in Bergen, Norway. The subjects were from all regions in Norway and were consecutively included in the project during the years of 2013–2015. Patients were included, examined, and evaluated based on the severity and duration of symptoms, both for pain and dysfunction and for consequences. Six specialists representing several disciplines, who created an individual treatment proposal for each patient, performed the examination. The investigation included pain intensity and duration, functional impairment (general and jaw-specific), effect on quality of life, and presence of extended periods of sick leave. Inclusion criteria were long-term TMD-related pain. Furthermore, inclusion was based on the examination; thus, patients with and without functional impairment were included. Exclusion criteria were non–TMD-related orofacial pain, relevant drug dependence problems, and obvious psychiatric diagnoses.

A healthy sex- and age-matched control group ($n = 60$) was recruited for comparison with the TMD patients, during 2016. A majority of the control group consisted of employees and students from the Department of Clinical Dentistry at the University of Bergen, who were not affiliated with the study research group. The remaining members of the control group were recruited from the general population in Bergen, Norway. The subjects gave their informed consent to participate in the study. Inclusion criteria for the control group was age 20 years or older and age- and sex-matched with the TMD patient group. Exclusion criteria were TMD symptoms or other musculoskeletal pain and symptoms in the head and neck area. Individuals in the control group were anonymized.

2.3. Questionnaire. TMD patients completed a comprehensive questionnaire prior to clinical examination. The questionnaire covered medical history, socioeconomic history, and lifestyle factors and included tools to assess psychosocial factors, specifically the Hospital Anxiety and Depression Scale (HADS) [18] and a 2-item version of the Coping Strategies Questionnaire [19] regarding catastrophizing. The healthy individuals completed a shortened version of the same questionnaire.

2.4. Saliva Samples and Analyses. Saliva samples were collected in the morning with the Salivette Cortisol Code Blue test kit (Sarstedt Darmstadt, Germany) and stored at −80°C until analysis. F and E were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at the Core Facility for Metabolomics, University of Bergen. Sample processing was completely robotized (Hamilton Robotics, Inc., Reno, NV, USA). Briefly, 20 μL of internal standard (Cortisol-2,3,4-$^{13}C_3$) was added to 100 μL of human saliva, which was subjected to liquid-liquid extraction with 480 μL of ethylacetate-heptane (80 : 20, v/v). The supernatant (380 μL) was subsequently washed with 50 μL of sodium hydroxide (0.1 M). Next, 280 μL of supernatant was removed and evaporated to dryness under nitrogen flow and then reconstituted in 100 μL of a 0.01% aqueous solution of formic acid : methanol (50 : 50, v/v). Samples were then analyzed on a Waters ACQUITY UPLC system connected to a Waters Xevo TQ-S tandem mass spectrometer (Waters, Milford, MA, USA). The compounds were separated on a C-18 BEH phenyl column from Waters (100 × 2.1 mm column, 1.7 mm particle size), which was developed by gradient elution over 5.5 min, using an aqueous solution of formic acid and acetonitrile as mobile phases. Formic acid adducts were detected in negative multiple reaction-monitoring mode. A potential source of bias is that the TMD patients likely experienced more stress prior to the examination compared to the controls because the majority of the controls were examined at their ordinary workplace.

2.5. Statistical Analyses. All statistical analyses were performed in STATA. Mean, median, range, and standard deviation (SD) for all variables in both groups were calculated. A paired t-test was used to calculate the P value of no difference in F, E, F/E ratio, and $F + E$ between the TMD group and the control group. A Wilcoxon signed rank test was used to calculate the P value of no difference in HADS and catastrophizing scores between the TMD group and the

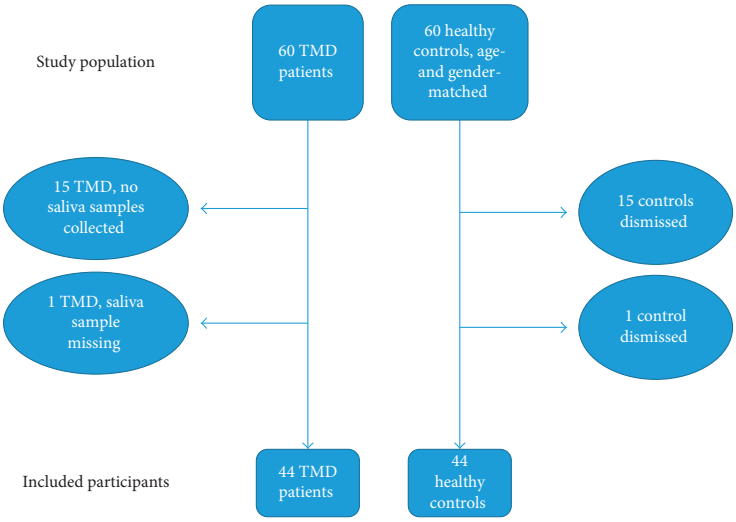

Figure 1: Flow chart of the study population: TMD patients and healthy controls.

control group. A linear multiregression between F and psychosocial factors in both groups was performed as well as a linear correlation (R) with associated P values between GC levels and psychosocial factors.

3. Results

3.1. Demographic Data. The multidisciplinary investigation [17] consisted of 60 patients, all experiencing severe TMD symptoms, and 60 healthy control subjects. Because no saliva sampling was done for the first 15 TMD patients and one saliva sample was missing from the patient group, the population in the present study ended up with 44 TMD patients and 44 healthy controls (Figure 1). The patients were aged 20–69 years, with a mean age of 44 years. The control subjects were aged 23–71 years with a mean age of 46 years. Both groups consisted of 38 women and 6 men.

3.2. Saliva Samples and Analyses. The TMD patient group had a mean saliva-sampling time point of 2 h, 52 min after awakening. The saliva samples were mostly collected at 9:00 AM but a few were collected at 11:00 AM owing to logistic factors. All subjects in the control group collected saliva 2 h, 45 min after awakening, matching the mean sampling time of the TMD patient group. Saliva samples from the control group were collected between 8:00 AM and 10:00 AM.

The transitions monitored under LC-MS/MS analyses were 405.22→329.24 for E and 407.24→331.26 for F. The linearity range was 0.7–100 nmol/L for E and 0.3–50 nmol/L for F. Accuracy was between 87% and 110%, and total imprecision was <10%.

3.3. Stress Scores and Glucocorticoids in Saliva. Our most important finding was that F in saliva was significantly higher in the TMD group compared to the control group ($P = 0.01$) (Table 1). E ($P = 0.04$), the F/E ratio ($P = 0.002$), and the sum of GC ($F + E$) in saliva ($P = 0.02$) were also significantly higher in the TMD group. Stress scores from questionnaires were significantly higher in the TMD group, including pain catastrophizing ($P < 0.0001$) and HADS ($P < 0.0001$) (Table 2). Pain catastrophizing score in the TMD group was negatively correlated with E and $F + E$ ($P = 0.033$ and $P = 0.047$, resp.); however, no association between F and pain catastrophizing was found (Table 3). In the control group, we observed a significant correlation between depression score and $F + E$ ($P = 0.045$). No other associations between the GC levels in saliva and psychosocial factors were found in the control group (Table 4).

4. Discussion

In this study, we found that F and E levels in saliva are significantly higher in TMD patients compared to healthy individuals. Our results were obtained by LC-MS/MS analysis. Compared with immunoassays, LC-MS/MS has much higher specificity and thus permits identification and quantification of F and E [16, 20, 21]. To our knowledge, this study is the first to determine F in TMD by LC-MS/MS and the first to investigate the sum and ratios of different GCs in TMD patients. However, the LC-MS/MS indicates significantly lower F levels than immunoassays due to a lower incidence of cross-reactions [22]. The correlation between LC-MS/MS and immunoassays is poor [16], and the F and E levels measured in this study are consequently not directly comparable to those from previous studies of TMD patients using immunoassays. Accordingly, our study may also contribute to the general assessment of salivary levels of F and E in healthy and diseased subjects.

F levels in healthy individuals follow circadian fluctuations. The lowest value occurs during early sleep and levels

Table 1: Glucocorticoid levels in saliva of TMD patients and healthy controls, analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). A paired *t*-test resulted in significant higher levels of cortisone (*E*) and cortisol (*F*), as well as the ratio of *F*/*E* and the sum of *F* + *E*, in TMD patients.

Glucocorticoids	Cortisone (*E*) (nmol/L)	Cortisol (*F*) (nmol/L)	*F*/*E* (ratio)	*F* + *E* (nmol/L)
TMD ($n = 44$)				
Mean	26.31	7.17	0.26	33.48
Median	24.83	6.29	0.26	31.37
Range	13.17–47.05	2.24–27.04	0.14–0.66	15.41–67.77
SD	8.61	4.56	0.09	12.49
Control ($n = 44$)				
Mean	22.91	4.90	0.20	27.81
Median	21.56	3.81	0.18	25.35
Range	10.54–74.38	1.42–28.21	0.10–0.53	15.68–102.59
SD	9.74	4.37	0.09	13.91
P value (paired *t*-test)	0.041	0.01	0.002	0.02

Table 2: Results from the questionnaires Hospital Anxiety and Depression Scale (HADS) and Coping Strategies Questionnaire regarding catastrophizing, assessed in the TMD patients and controls. A signed rank test resulted in significant higher score on all parameters in the TMD patient group.

Psychosocial scores	Mean	Median	Range	SD	*P* value (signed rank)
Catastrophizing (0–12)					<0.0001
TMD	7.88	8.0	1–12	2.95	
Control	1.39	0.0	0–11	2.64	
Anxiety (*A*) (0–21)					0.0002
TMD	7.73	7.0	0–20	5.11	
Control	3.35	2.0	0–12	3.22	
Depression (*D*) (0–21)					<0.0001
TMD	6.28	5.0	0–19	5.07	
Control	1.70	1.0	0–9	2.32	
A + *D* (HADS) (0–42)					<0.0001
TMD	14.25	13.0	0–39	9.76	
Control	5.05	3.5	0–19	4.85	

rise until awakening and then rise even faster in the cortisol awakening response. The peak value occurs approximately 30–45 min after awakening [23, 24]. Our saliva samples had a mean sampling time 2 h, 52 min after awakening in the TMD group and 2 h, 45 min in the control group. Accordingly, *F* levels from our patients and controls were not directly comparable to previous TMD studies because of the diurnal decrease in *F* levels after peaking in addition to lower *F* levels being expected from LC-MS/MS compared with immunoassays.

Many studies have reported elevated *F* levels in TMD patients compared to healthy individuals. A significantly higher daytime *F* value in plasma was reported in subjects with TMD compared to healthy controls [14]. Analysis of saliva from TMD patients also revealed elevated *F* levels [11, 12]. Significant higher *F* levels as a response to experimental stress in subjects with TMD has also been reported [15]. In contrast, some researchers have not found significant differences in salivary *F* levels related to TMD [13]. In a study examining hair *F* concentration, even lower values of *F* were found in subjects with TMD [7].

Elevated or lowered basal *F* levels may reflect changes in the regulation of the HPA axis, which is discussed in other TMD studies and in several studies of stress-related and chronic pain disorders [7, 9, 14, 15, 25–32]. A significantly higher rise in salivary *F* in response to experimental stress has been reported in a TMD group compared to a healthy control group [15]. An opposite finding within a subgroup separate from the TMD group in the same study showed slightly lower, but nonsignificant, salivary *F* levels compared to the control group at all measuring points. No significant differences in basal *F* levels existed between the TMD and control groups before the stress exposure [15]. However, no difference in salivary *F* levels was reported as a response to experimental pain in a TMD group compared to a control group. Nevertheless, an association between high pain-catastrophizing scores and high *F* response to pain was observed although basal morning *F* was lower in association with high pain catastrophizing in both TMD and controls [25]. In our study, we showed that not only *F*, but also *E* and the sum of both GCs (*F* + *E*), was significantly higher in the TMD group. This finding means that the total sum of GCs is higher in the TMD group and supports the theory of an upregulated HPA axis, with higher *F* secretion from adrenal cortex. The high level of the inactive hormone *E* may be the result of enzymatic conversion of *F* by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) in the glandula parotis.

Table 3: Linear correlation (R) with associated P values between glucocorticoid levels and psychosocial factors in the TMD group. Pain-catastrophizing score was significant, negatively correlated with E and the sum of glucocorticoids ($F + E$) ($P = 0.033$ and $P = 0.047$, resp.). No significant association between F and pain catastrophizing was found, neither any significant associations between the other parameters of glucocorticoid levels in saliva and psychosocial factors.

TMD group	Cortisone (E)	Cortisol (F)	F/E-ratio	$F + E$
Catastrophizing score				
R	−0.323	−0.230	−0.080	−0.305
P value	0.033	0.138	0.611	0.047
Anxiety (A) score				
R	−0.089	0.125	0.247	−0.016
P value	0.566	0.420	0.107	0.919
Depression (D) score				
R	−0.091	0.036	0.128	−0.049
P value	0.563	0.821	0.415	0.753
$A + D$ (HADS) score				
R	−0.042	0.123	0.211	0.016
P value	0.785	0.426	0.169	0.919

Table 4: Linear correlation (R) with associated P values between glucocorticoid levels and psychosocial factors in the control group. Depression score was significantly associated with the sum of glucocorticoids ($F + E$) ($P = 0.045$). No significant associations between the other parameters of glucocorticoid levels in saliva and psychosocial factors were observed.

Control group	Cortisone (E)	Cortisol (F)	F/E-ratio	$F+E$
Catastrophizing score				
R	0.111	0.147	0.175	0.124
P value	0.473	0.340	0.256	0.422
Anxiety (A) score				
R	0.187	0.171	0.044	0.185
P value	0.225	0.266	0.778	0.231
Depression (D) score				
R	0.313	0.269	0.010	0.304
P value	0.039	0.077	0.519	0.045
$A + D$ (HADS) score				
R	0.273	0.242	0.077	0.268
P value	0.073	0.113	0.620	0.079

Another possible explanation of higher F levels in TMD patients may arise from suppressed negative feedback of the HPA axis, as seen in major depression [27]. An exaggerated F response to CRH as well as higher basal F levels has been reported for patients with irritable bowel syndrome [28]. Since we did not perform any suppression tests in our study, we could not evaluate the negative feedback of the HPA axis for comparison.

The F/E ratio is an indicator of 11β-HSD activity, which has previously been measured in early morning saliva sample and found to be 0.24 [33], 0.15 [34], and 0.20 [35]. The active molecule F is converted to an inactive form E in parotid tissue by the enzyme 11β-HSD-1 and a reverse conversion by 11β-HSD-2. Our calculations resulted in a F/E ratio of 0.26 in TMD patients compared to 0.2 in controls. The difference may be explained by decreased activity of 11β-HSD-2 in TMD patients or 11β-HSD-2 saturation at a high substrate concentration [35]. Enzyme saturation has previously been indicated by scatter plots with curve fitting [33, 35], showing that the increase in salivary E is nonlinear with the increase of salivary F at high F concentrations. For example, an elevated F/E ratio was reported in a study of apparent mineralocorticoid excess [36], and F/E ratios in urine were reported to be significantly higher in depressed patients compared to healthy individuals [37]. In fetoplacental tissue, 11β-HSD-2 has a key function in neurobehavioral development, and loss of its function has resulted in lifelong anxiety in mice [38]. Given that 11β-HSD-2 is supposed to protect the mineralocorticoid receptor from GC binding [39], examining blood pressure in TMD patients in future studies could be interesting.

Psychosocial factors such as stress, anxiety, and depression may influence the HPA axis as well, although the response seems unclear and inconsistent. Stress may potentially be an important factor in the etiology of TMD [11]. The prevalence of physical and psychological stressors in TMD is high, and they may contribute to dysregulation of the HPA axis [8]. However, no significant differences in salivary morning F were reported from a study of 30 young women with TMD, although the TMD subjects appeared more psychologically distressed compared to healthy individuals [13]. Subjects with TMD also had a significantly higher stress score, despite apparently lower F levels, which were measured through hair analysis [7]. However, F levels in hair may reflect stress and F output over time, while salivary F reflects the same variables at the point of measurement. The TMD patients in our study scored significantly higher on HADS and pain-catastrophizing questionnaires, which could reflect higher stress levels that potentially contribute to an upregulation of the HPA axis. Still, we did not find any significant correlation between anxiety, depression, or catastrophizing scores and F levels. This outcome may be due to the presence of many other factors influencing F levels. Nevertheless, we found a significantly negative association between pain-catastrophizing score and both E and the sum of GCs ($F + E$). F was also lower with higher pain catastrophizing in the TMD group, but the association was nonsignificant. Nevertheless, the findings from our study are comparable with a previous study in which lower basal F was associated with high pain catastrophizing [25]. Nonsignificantly higher catastrophizing scores in a subgroup of TMD patients with low F levels have also been reported [15]. However, we did not see lower F levels correlated to anxiety or depression in the TMD group. In the control group, we observed a significant correlation between depression score and $F + E$, though the majority in the control group had a depression score that ranged zero to very low, and the association has probably low scientific value. We could not find any other correlations

between GC levels and any psychological factor in the control group. A recent review on stress in chronic pain patients highlighted that several types of HPA-axis dysregulation can occur in chronic stress and pain conditions, leading to a HPA-axis stress response that cannot be determined by basal *F* levels only [40].

The role of stress in the etiology of TMD remains unclear. The effect of stress in TMD patients may result in a complex and multifactorial response by biological systems, including neuroendocrine function and psychosocial and physical adjustments [9].

5. Conclusion

In summary, we report that a group of TMD patients had significantly higher *F* and *E* levels compared to a healthy control group. This finding may indicate that TMD patients have an upregulated HPA axis. Anxiety/depression and pain-catastrophizing scores were significantly higher in the TMD group, and they may potentially indicate chronic upregulation of the HPA axis. Based on these results, the hypothesis that TMD patients have an upregulated HPA axis may be approved. More research is needed to confirm the activity of the HPA axis in TMD patients. In future studies, it would be interesting to collect samples at several time points to compare their diurnal *F* rhythm. Examination of the *F* response to experimental stress would be expedient, as would suppression by dexamethasone and further investigation of 11β-HSD; blood pressure would be of great interest.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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Research Article

Serum Analysis in Patients with Temporomandibular Disorders: A Controlled Cross-Sectional Study in Norway

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Temporomandibular disorder (TMD) is characterized by pain and dysfunction in the temporomandibular join (TMJ) and the masticatory apparatus. Associations with autoimmune diseases, inflammatory conditions, and nutrition deficiencies have been reported in previous studies of TMD patients. To evaluate essential proteins, hormones, electrolytes, and vitamins in serum from TMD patients, a standard blood sample analysis was performed in 60 TMD patients and 60 healthy controls matched for age and gender, retrieving 19 different analyses. We found that TMD patients had significantly higher values of hemoglobin ($p = 0.036$), cobalamin ($p = 0.023$), albumin ($p = 0.005$), parathyroid hormone (PTH) ($p = 0.038$), and vitamin D ($p = 0.005$), and significantly lower values of creatinine ($p = 0.006$) and potassium ($p = 0.011$), compared to controls. In the TMD group, most of the determinants had a wider range, and several subjects, compared to the control group, had values outside the normal reference area. However, most of the TMD patients and controls had values within normal biological range. Our findings could not associate any severe systemic disease, malnutrition, or systemic inflammation with the TMD. Results from our study suggest that serum analyses should neither be used as a biomarker of TMD nor a diagnostic tool for an individual subject with TMD.

1. Introduction

Temporomandibular disorder (TMD) is characterized by pain and dysfunction in the masticatory apparatus and the temporomandibular joint (TMJ). A significant higher prevalence of comorbidities, such as degenerative arthritis, gastrointestinal symptoms, fibromyalgia, depression, and fatigue, has been revealed in this group of patients [1]. Autoimmune diseases and inflammatory conditions have been associated with TMJ disease (TMJD) in a recent hospital-based case-control study [2]. Summary from the Prospective Evaluation and Risk Assessment (OPPERA) project describes the etiology of TMD as complex and multifactorial, where pain sensitivity, biopsychosocial effects, and comorbidity are some of the contributing factors [3]. The prevalence of TMD is higher in women, who had a two-time higher risk in development of TMD compared to men [4]. In addition, pain intensity has been reported to be greater in women compared to men [5].

In TMD patients, few studies analyzing health status in serum have been published previously. Significantly, higher levels of parathyroid hormone (PTH) have been observed in TMD patients compared to a control group [6]. Patients with TMD as well as TMJD showed high prevalence of nutrition deficiencies, including iron, ferritin, vitamin D, vitamin C, vitamin B1, vitamin B6, vitamin B12, and folate [7, 8]. High levels of C-reactive protein (CRP) have been associated with inflammation in the TMJ in patients with rheumatoid arthritis (RA) [9]. On the other hand, no difference in levels of CRP was reported in patients with persistent TMJ pain, compared to controls [10]. Low levels of vitamin D have been associated with incidence of chronic pain [11] and chronic pain-related comorbidities, including sleep deprivation and depression [12]. One study revealed a high

prevalence of vitamin D deficiencies in TMD patients; however, there were no significant differences in vitamin D or calcium levels in those patients compared to a control group [6].

Levels of the current hormones, electrolytes, and vitamins can easily be detected by blood sampling. Standardized serum tests can be used in diagnostics and evaluation of patient's health to detect diseases [13]. Laboratory serum analyses are also useful in revealing inflammation and autoimmune diseases and may indicate severity of the disease [14].

To our knowledge, the present study is the first to reveal as many as 19 different determinants in serum from TMD patients at the same time. The primary aim of the present study was to evaluate essential proteins, hormones, electrolytes, and vitamins in serum from TMD patients. Our hypothesis is that TMD patients have significantly different values of essential proteins, hormones, electrolytes, and vitamins in serum, compared to a healthy control group, and this may influence TMD symptoms.

2. Materials and Methods

2.1. Study Design. The present study was a controlled cross-sectional study, as part of a multidisciplinary investigation of TMD patients at Haukeland University Hospital (HUS) in Bergen, Norway [15]. Six different specialists including two dental specialists, one anesthesiologist, one psychologist, one physiotherapist, and one radiologist examined the patients. Pain-related symptoms and dysfunction (both general and TMD-related), general health status, psychosocial factors, previous treatment and medication, and the duration of pain and disease were disclosed.

Ethical approval was granted by the Regional Ethical Review Board South East (2015/930), in accordance with the Helsinki Declaration (1964). All subjects submitted written informed consent as a prerequisite for participating in the study.

2.2. Participants. The study population consisted of 60 TMD patients with severe symptoms and long-term pain and 60 healthy controls matched for age and gender. A previous study regarding stress and HPA axis regulation, involving the majority of the present study group, has been published [16]. The TMD patients were referred by their general practitioner (GP) to the project from all health regions in Norway, during the years 2013–15, and were clinically examined and evaluated consecutively. Patients were included, examined, and evaluated based on the severity and duration of symptoms, both for pain and dysfunction and for consequences. The six specialists at HUS, representing several disciplines, performed the examination and created an individual treatment proposal for each patient. The investigation included pain intensity and duration, functional impairment (general and jaw-specific), effect on quality of life, and presence of extended periods of sick leave. The inclusion criterion was long-term TMD-related pain. Furthermore, inclusion was based on the examination; thus, patients with and without functional impairment were included. The exclusion criteria were non-TMD-related orofacial pain, relevant drug dependence problems, and obvious psychiatric diagnoses. A healthy age- and gender-matched control group was recruited and examined during 2016.

The control group consisted of employees and students from the Department of Clinical Dentistry at the University of Bergen and was not a part of the study research group; additionally, there were a few subjects from the general population in Bergen. The inclusion criterion was age- and gender-matched with the patient group. The exclusion criteria were TMD symptoms, musculoskeletal pain, and symptoms in the head and neck area.

2.3. Serum Analyses. A standard blood sample analysis was conducted at Haukeland University Hospital and analyzed at the Laboratory for Clinical Biochemistry. The serum analyses retrieved 19 different analyses consisting of essential proteins, hormones, electrolytes, and vitamins. Those were hemoglobin (Hb), erythrocyte volume fraction (EVF), mean corpuscular volume (MCV), homocysteine, transferrin receptor (TfR), thyroid stimulating hormone (TSH), free thyroxine (FT4), parathyroid hormone (PTH), cobalamin, folate, C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (GFR), sodium, potassium, calcium, gamma-glutamyl transferase (GT), albumin, and 25 (OH) vitamin D3 (vitamin D). CRP levels lower than 1 mg/L were registered as 1 mg/L due to limitations in the laboratory.

2.4. Statistical Analyses. Statistical analyses were performed in STATA. Mean, range, and standard deviation (SD) were calculated for all variables in both groups. Since our study matched age and gender between the groups, paired t-tests were appropriate to calculate p-value of no difference in all determinants from the serum analyses between the TMD group compared to the control group and between subgroups of women and men in the TMD group compared to women and men control group. Linear correlations (R) with associated p-values between CRP and pain parameters and between vitamin D and pain parameters, as well as between vitamin D and PTH, were calculated in both groups.

3. Results

3.1. Demographic Data. The group of 60 TMD patients consisted of 51 women and 9 men, all affected with severe TMD symptoms. Mean pain duration in the patient group was 11 years (ranged 1–40 years). Mean age of the patient group was 45 years (ranged 20–69 years). Registered diagnoses on our clinical examination of the TMD group were fibromyalgia ($n = 8$), migraine ($n = 12$), and chronic fatigue ($n = 4$). The control group was matched for age and gender and had a mean age of 46 years (ranged 23–71 years). The study population is presented in Figure 1.

3.2. Serum Analyses. Results revealed that TMD patients had significantly higher values of hemoglobin ($p = 0.036$),

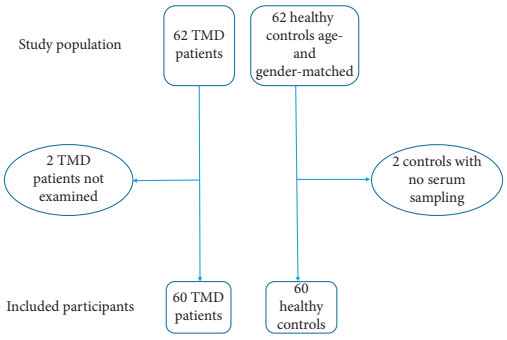

Figure 1: Flow chart of the study population: TMD patients and healthy controls.

cobalamin ($p = 0.023$), albumin ($p = 0.005$), parathyroid hormone (PTH) ($p = 0.038$), and vitamin D ($p = 0.005$), and significantly lower values of creatinine ($p = 0.006$) and potassium ($p = 0.011$), compared to controls (Table 1). Further, gender-matched analyses of TMD patients and controls showed that in the TMD patient group only albumin was significantly higher in both women (($p = 0.017$) and men ($p = 0.026$). In women with TMD, significantly higher values of hemoglobin ($p = 0.045$), cobalamin ($p = 0.020$), PTH ($p = 0.040$), and vitamin D ($p = 0.002$), as well as significantly lower values of creatinine ($p = 0.018$) and potassium ($p = 0.002$), were observed. In men with TMD, significantly higher values of TSH ($p = 0.040$) were observed (Table 2). Further details of serum levels outside normal reference values in both groups are presented in Table 3. Low levels of vitamin D were significantly correlated ($p = 0.002$) with high levels of PTH in the control group, however nonsignificant in the patient group (Figure 2).

3.3. Medications. Regular medications used by the patients were paracetamol ($n = 28$), NSAIDs ($n = 23$, hereunder celecoxib in one patient), opioids ($n = 20$, hereunder strong opioids in 5 patients and weak opioids in 17 patients), antidepressants ($n = 15$, hereunder tricyclic antidepressants in 7 patients and selective antidepressants in 10 patients), zopiclone ($n = 7$), clonazepam ($n = 3$), gabapentinoids ($n = 6$, hereunder gabapentin in 4 patients and pregabalin in 2 patients), carbamazepine ($n = 1$), and topiramate ($n = 1$). Serum levels of calcium and creatinine were normal in patients who used celecoxib, pregabalin, and topiramate and were within normal reference values. One patient who used carbamazepine had slightly elevated levels serum TfR (5.7 mg/L) and normal serum levels of serum Hb.

4. Discussion

Based on the results of the present study, we were unable to associate any severe systemic disease, malnutrition, or systemic inflammation with TMD. We performed nineteen different, common diagnostic serum analyses determining essential proteins, hormones, ions, and vitamins, and most of the TMD patients and controls showed values within normal biologic range. Medications used by the patients were not found to have any major impact on serum analyses. Findings from our study support results from the OPPERA project, suggesting that TMD is a complex disorder influenced by psychosocial factors and pain sensation rather than being a state of disease indicated by analyses of serum compounds [3]. Supporting observations have also been reported, currently, regarding levels of vitamin D and calcium [6]. Nonsupporting studies have shown a high prevalence of malnutrition including deficiencies in vitamin D, vitamin B, and iron in a population of TMD patients [7], as well as a high prevalence of low serum vitamin B, folate, and iron [8].

An unexpected result revealed that the control group had significantly lower values of vitamin D compared to the TMD group. In both groups, deficiency in D vitamins was commonly observed. A high prevalence of vitamin D deficiencies in both TMD patients and healthy controls [6], as well as healthy individuals [17], has also been reported previously. Nearly one half of TMD patients in Saudi population were also reported to have low vitamin D levels, although there was no control group for comparison [7]. In nonspecific musculoskeletal persistent pain, vitamin D deficiency was observed in the majority of all patients, implying that there is a link between chronic pain and vitamin D deficiency [18]. Prevalence of vitamin D deficiencies has been observed to be higher in patients with chronic pain [11] and has also been associated with chronic widespread pain in a meta-analysis [19]. Vitamin D supplements, in some studies, have been linked with alleviation of chronic pain [11]. Vitamin D has also been suggested to have a function in the maintenance of chronic pain and associated comorbidities through hormonal, immunological, and neurological influences [12]. In a randomized controlled trial of fibromyalgia patients, normalization of vitamin D levels was associated with a decrease in pain intensity measured on a visual analog scale (VAS) [20]. On the other hand, results from a meta-analysis failed to prove the effect of vitamin D supplementation on pain in subjects with chronic musculoskeletal pain [21]. It also appears that vitamin D deficiency is quite common in the healthy population and varies throughout the year [17, 22]. The difference of lower vitamin D levels in our control group could potentially be explained by three factors. First is the geographic factor; all subjects in the control group lived in Bergen, where the number of hours of sun per year is very low, while the TMD patients were from all over the country of Norway. The second factor is that TMD patients probably consult with their GP more often and get their nutritional serum levels analyzed more often compared to the healthy individuals. The third factor is that more subjects in the TMD group probably take overdoses of nutritional supplements, as confirmed by the outcome from our investigation.

Parathyroid hormone (PTH) was significantly higher in the TMD group of the present study. However, both elevated and lowered levels of PTH were observed in the TMD patient group on the individual level. A high level of PTH reflects hyperparathyroidism, while low levels reflect

Table 1: Serum analyses resulted in nineteen different determinants common in diagnostics. Second column shows normal values for women and men at all ages. Most TMD patients and controls had values within normal biologic range. TMD patients had significantly higher values of hemoglobin ($p = 0.036$), cobalamin ($p = 0.023$), albumin ($p = 0.005$), PTH ($p = 0.038$), and vitamin D ($p = 0.005$) and significantly lower values of creatinine ($p = 0.006$) and potassium ($p = 0.011$) compared to controls.

Serum analyses	Reference values	TMD			Control			p-value (paired t-test)
		Mean	±SD	Range	Mean	±SD	Range	(* = sign.)
Hemoglobin	*W*: 11.7–15.3, *M*: 13.4–17.0 g/dL	14.1	1.28	8.1, 16.2	13.8	0.83	11.5, 16	0.036*
EVF	*W*: 0.35–0.46, *M*: 0.40–0.50	0.41	0.04	0.28, 0.48	0.41	0.02	0.35, 0.48	0.325
MCV	82–98	91.2	4.66	76, 102	90.1	3.62	83, 100	0.299
Homocysteine	<15 umol/L	11.1	3.79	5.8, 28.0	11.3	3.03	5.7, 24.2	0.459
Transferrin R	*W*: 1.9–4.4, *M*: 2.2–5.0 mg/L	3.27	1.78	1.7, 14.6	2.98	0.80	1.7, 5.9	0.103
TSH	0.4–4.5 mlE/L	1.63	0.83	0.01, 4.31	1.80	0.98	0.14, 4.72	0.191
FT4	9.5–22.0 pmol/L	16.0	3.13	7.8, 29	15.7	2.26	11.5, 27.0	0.266
Cobalamin	175–700 pmol/L	422	194.8	167, 1322	363	124.9	129, 702	0.023*
Folate	>8 nmol/L	20.7	10.41	7.7, 45.3	20.2	7.38	7.5, 45.3	0.450
CRP* (<1 = 1)	<5 mg/L	2.43	3.09	1.0, 14.0	2.10	2.84	1.0, 20.0	0.268
Creatinine	*W*: 45–90, *M*: 60–105 umol/L	65.6	10.47	45, 93	69.7	12.14	49, 108	0.006*
Estimated GFR	>90 mL/min/l	>60	—	—	>60	—	—	—
Sodium	137–145 mmol/L	140.1	1.48	137, 144	140.0	1.39	136, 144	0.227
Potassium	3.5–5.0 mmol/L	4.0	0.25	3.2, 4.6	4.1	0.31	3.4, 5.3	0.011*
Calcium	2.20–2.55 mmol/L	2.40	0.09	2.21, 2.63	2.40	0.08	2.15, 2.59	0.456
GT	*W*: <40y = 10–45, >40y = 10–75 U/L *M*: <40y = 10–80, >40y = 15–115 U/L	22.2	19.63	8.0, 145.0	17.9	12.20	6.0, 72.0	0.078
Albumin	<39y: 39–50, 40–69y: 39–48, >70y: 36–48 g/L	46.3	2.94	40.0, 53.0	45.1	1.96	40.0, 49.0	0.005*
PTH	1.3–6.8 pmol/L	3.4	1.53	0.9, 8.2	2.9	1.09	1.0, 6.0	0.038*
Vitamin D	50–113 nmol/L	72.4	26.93	19.0, 187.0	61.1	18.68	22.0, 127.0	0.005*

hypoparathyroidism. Elevated levels of PTH in TMD patients compared to healthy controls have previously been reported [6], where the majority of TMD patients had elevated PTH levels, primarily described as a response to low vitamin D levels. The level of PTH in depressed patients has also been demonstrated to be significantly higher compared to controls [23]. On the other hand, a clinical study examining hyperparathyroidism in patients with fibromyalgia, widespread pain, and localized musculoskeletal pain concluded there were no differences in prevalence between the groups nor compared to the general population [24]. A few patients in the present study also had elevated levels of free thyroxine (FT4), which may reflect hyperthyroidism. A recent clinical case-control study reported a significantly higher prevalence of TMD symptoms as well as the severity of symptoms in patients with Hashimoto thyroiditis (HT) compared to healthy control subjects [25]. HT goes through several stages from hyperparathyroidism to hypoparathyroidism, and its main symptoms are like TMD, including musculoskeletal pain and stiffness. The fact that thyroid hormones play an important role in muscle function [26] is supported by the common occurrence of neuromuscular symptoms [27] and musculoskeletal disorders [28] in patients with thyroid dysfunctions. Thyroid disease has also previously been associated with idiopathic tongue pain in a clinical study [29]. Observed levels of PTH in the present study may possibly reflect some prevalence of parathyroid disturbances or disturbances in the hormonal thyroid-regulating pathways in the TMD group. However, there was no overall significant difference in thyroid stimulating hormone (TSH), nor in FT4, between the TMD patient group and the control group. An exception was observed in the subgroup of male TMD patients, who had significantly higher levels of TSH compared to the subgroup of male controls.

Elevated PTH is often seen in association with low vitamin D, leading to elevated calcium absorption from bone [22]. Similarly, we observed a significant negative association between PTH levels and vitamin D levels in the control group but not in the patient group. The observed association may be explained by the fact that vitamin D levels were lower in the control group, resulting in higher stimulation of excretion of PTH, compared to the patient group. A supporting observation from a laboratory database study, examining the association between serum PTH and vitamin D levels in 19,172 subjects in the Israeli population, concluded that vitamin D levels had to be below the reference value of 50 nmol/L to sufficiently elevate PTH levels [30]. A noteworthy finding considering vitamin D and PTH levels in the present study was that most subjects in both groups had normal values of calcium. Elevated vitamin D and PTH in the presence of normal calcium values were also observed in a previous study of TMD patients [6]. A possible explanation could be that normalized levels and intake of calcium may suppress the increase of secretion of PTH, when vitamin D is low [17].

There were no significant differences in CRP levels between the TMD group and the control group. Mean CRP levels have previously been observed within the normal range in patients with TMJD and were not affected by pain [10]. The fact that most TMD patients have normal values of CRP means that the pain intensity is probably not directly associated with inflammation. However, some patients in

Table 2: Gender-matched serum analyses: Results from serum analyses showed mean levels statistically differed between TMD patients and controls, divided into subgroups of women and men. The second column shows normal values for women and men at all ages. Significantly higher levels of hemoglobin ($p = 0.045$), cobalamin ($p = 0.020$), albumin ($p = 0.017$), PTH ($p = 0.040$), and vitamin D ($p = 0.002$) were observed in women in the TMD group. Significantly lower levels of creatinine ($p = 0.018$) and potassium (0.002) were observed in women in the TMD group. Significantly higher levels of TSH ($p = 0.040$) and albumin ($p = 0.026$) were observed in men in the TMD group. The number of men was considerably smaller in both groups.

Gender-matched serum analyses	Reference values	TMD ($n = 60$)			Control ($n = 60$)			p-value (paired t-test)
		Mean	±SD	Range	Mean	±SD	Range	(* = sign.)
Hemoglobin								
Women ($n = 51 + 51$)	11.7–15.3 g/dL	13.9	1.22	8.1, 15.7	13.6	0.70	11.5, 14.7	0.045*
Men ($n = 9 + 9$)	13.4–17.0 g/dL	15.2	1.13	13.4, 16.2	14.9	0.62	14.0, 16.0	0.288
TSH								
Women ($n = 51 + 51$)	0.4–4.5 mlE/L	1.52	0.82	0.01, 4.31	1.80	1.04	0.14, 4.72	0.111
Men ($n = 9 + 9$)	0.4–4.5 mlE/L	2.24	0.59	1.25, 3.34	1.84	0.52	1.17, 2.49	0.040*
Cobalamin								
Women ($n = 51 + 51$)	175–700 pmol/L	425	210.0	167, 1322	355	128.4	129, 702	0.020*
Men ($n = 9 + 9$)	175–700 pmol/L	401	60.67	310, 455	403	100.3	291, 568	0.483
Creatinine								
Women ($n = 51 + 51$)	45–90 umol/L	62.8	8.01	45, 81	66.2	8.77	49, 84	0.018*
Men ($n = 9 + 9$)	60–105 umol/L	81.3	8.93	68, 93	88.9	9.97	74, 108	0.098
Potassium								
Women ($n = 51 + 51$)	3.5–5.0 mmol/L	4.0	0.25	3.2, 4.6	4.1	0.30	3.4, 5.3	0.002*
Men ($n = 9 + 9$)	3.5–5.0 mmol/L	4.1	0.21	3.9, 4.5	4.0	0.33	3.5, 4.5	0.267
Albumin								
Women ($n = 51 + 51$)	Age dependent <39y: 39–50, 40–69y: 39–48, >70y: 36–48 g/L	45.9	2.98	40.0, 53.0	44.9	1.91	40.0, 49.0	0.017*
Men ($n = 9 + 9$)		48.0	2.08	45.0, 51.0	46.6	1.59	44.0, 48.0	0.026*
PTH								
Women ($n = 51 + 51$)	1.3–6.8 pmol/L	3.5	1.58	0.9, 8.2	2.9	1.03	1.0, 5.2	0.040*
Men ($n = 9 + 9$)	1.3–6.8 pmol/L	2.7	1.10	1.1, 4.2	2.58	1.39	1.4, 6.0	0.385
Vitamin D								
Women ($n = 51 + 51$)	50–113 nmol/L	75.3	26.23	19.0, 187.0	61.8	19.78	22.0, 127.0	0.002*
Men ($n = 9 + 9$)	50–113 nmol/L	55.8	26.21	21.0, 111.0	57.6	11.02	42.0, 72.0	0.426

the present study had elevated CRP levels ranging from 5 to 20 mg/L that may potentially be enough to reflect a local inflammation. In a radiographic CT and MRI study of patients with rheumatoid arthritis (RA), mean CRP levels were between 10 and 20 mg/L, and the levels of CRP were also correlated with inflammation in the TMJ [9]. In other studies of patients diagnosed with RA, higher levels of CRP were correlated with resorbed condyles in the TMJ, seen on CT [31], and low jaw opening capacity [32]. In a large population of adults in the United States, elevated serum CRP was positively associated with pain and headache when assessed by questionnaires [33]. The fact that low income also was associated with pain and not with CRP indicates that CRP levels contributed to increased pain independent of pain-related social factors [33]. Albumin, which functions as a carrier protein and has a role in maintaining colloid osmotic pressure, was significantly higher in the TMD group. Elevated levels of albumin normally reflect dehydration. Moreover, high albumin levels have previously been associated with metabolic syndrome [34]. The fact that high levels of albumin have previously been negatively associated with pain [33] and significantly lower levels of inflammatory cytokines in healthy older subjects [35] indicates that high levels of albumin are not related to pain disorders. Since albumin was high in our group of TMD patients, systemic inflammation was also less likely.

Another indicator of high doses of nutritional supplementation in our group of TMD patients was significantly higher levels of cobalamin, possibly due to vitamin B12 supplementation. On the other hand, 10% of the TMD patients had elevated levels of homocysteine, even though there were no statistical differences in mean levels of homocysteine compared to the control group. High homocysteine levels reflect low levels of vitamin B12, vitamin B6, and folate, and the observed elevated levels in some patients may potentially be explained by the possibility of reduced intake of diet sources in the patient group because of jaw impairment and pain from chewing. However, there was no statistical difference in serum folate levels between the TMD patients and controls. A previous study of serum analyses in TMD patients reported a high prevalence of low vitamin B levels, including folate and vitamin B complex [7]. Similarly, a high prevalence of low vitamin B levels in patients with complex TMJ problems, including vitamin B1, vitamin B6, vitamin B12, and folate, was shown in another study [8].

In the TMD group, we observed some patients with elevated levels of transferrin receptor (TfR) and low

Table 3: Elevated and lowered values: observed number and percent of patients and controls with elevated and lowered values of the different determinants from the serum analyses. Mild to moderate vitamin D level deficiency was seen in 11 TMD patients compared to 18 controls. Furthermore, we observed marginally elevated levels of CRP ($n = 7$) and elevated levels of transferrin receptor ($n = 7$) and homocysteine ($n = 6$), as well as lowered levels of erythrocyte volume fraction (EVF) ($n = 5$), in the TMD group. FT4 was elevated in 3 patients and lowered in one patient, while parathyroid hormone (PTH) was elevated in 2 patients and lowered in 4 patients.

Elevated and lowered values	TMD				Control			
	Elevated		Lowered		Elevated		Lowered	
	n	%	*n*	%	*n*	%	*n*	%
Hemoglobin	1	1.7	2	3.3	0	0.0	1	1.7
EVF	1	1.7	5	8.3	0	0.0	0	0.0
MCV	1	1.7	3	5.0	4	6.7	0	0.0
Homocysteine	6	10.0	0	0.0	3	5.0	0	0.0
Transferrin R	7	11.7	3	5.0	3	5.0	2	3.3
TSH	0	0.0	2	3.3	1	1.7	1	1.7
FT4	3	5.0	1	1.7	1	1.7	0	0.0
Cobalamin	5	8.3	1	1.7	1	1.7	1	1.7
Folate	0	0.0	2	3.3	0	0.0	1	1.7
CRP	7	11.7	0	0.0	4	6.7	0	0.0
Creatinine	0	0.0	0	0.0	1	1.7	0	0.0
Estimated GFR	0	0.0	0	0.0	0	0.0	0	0.0
Sodium	0	0.0	0	0.0	0	0.0	1	1.7
Potassium	0	0.0	1	1.7	1	1.7	1	1.7
Calcium	1	1.7	0	0.0	3	5.0	1	1.7
GT	2	3.3	5	8.3	0	0.0	7	11.7
Albumin	9	15.0	0	0.0	0	0.0	0	0.0
PTH	2	3.3	4	6.7	0	0.0	1	1.7
Vitamin D	3	5.0	11	18.3	1	1.7	18	30.0

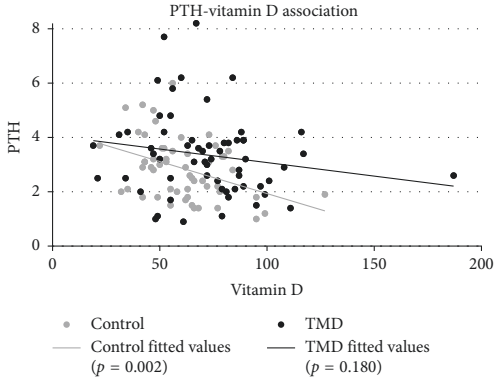

Figure 2: Linear correlation between parathyroid hormone and vitamin D in the TMD group (black) and the control group (grey). Low levels of vitamin D were significantly correlated ($p = 0.002$) with high levels of PTH in the control group; however, this correlation was nonsignificant in the patient group.

erythrocyte volume fraction (EVF), which potentially could indicate iron deficiency or an increase in erythropoiesis [36–38]. Iron deficiencies have previously been observed in TMD patients [7, 8]. Although, mean values of TfR and EVF in the present study did not statistically differ between TMD patients and controls, and the fact that hemoglobin was significantly higher in the TMD patient group supports the explanation of higher erythropoiesis. Serum TfR has previously been observed to be elevated in children with juvenile chronic arthritis, without any correlation to serum transferrin or ferritin levels, indicating that serum TfR is an inadequate indicator of iron levels in the presence of chronic inflammation [36].

The levels of creatinine were significantly lower in the TMD patient group. Creatinine is a degradation product of creatine phosphate, which has an important role in muscle function and fast energy production [39]. Low levels of serum creatinine may reflect muscle atrophy and has also been directly associated to low bone mineral density in subjects with normal renal function [40]. In a randomized controlled trial of patients with fibromyalgia, creatine supplementation resulted in significantly improved function of muscle; however, no improvements in pain or psychosocial factors were observed [41].

Potassium was significantly lower in the TMD group. Potassium homeostasis is regulated by renal and extrarenal mechanisms, affected by acid-base balance and hormonal regulation by epinephrine, insulin, and aldosterone [42]. The uptake and release of extracellular potassium is mainly mediated by the skeletal muscles through several $K+$ channels [43], contributing to maintain the extrarenal homeostasis. The fact that abnormal $K+$ channel activity has a role in chronic pain [44] makes it reasonable to suspect that changes in potassium homeostasis may affect the function of $K+$ channels in painful disorders. Despite the presence of statistically significantly lower levels of potassium in our group of TMD patients, the observed difference probably has no clinical value since most patients and controls had

normal potassium levels. A possible explanation of lower potassium levels in the patient group may be due to lower intake of fluid or electrolyte status. However, sodium levels were normal in all patients and did not statistically differ from the control group, indicating normal electrolyte balance.

The prevalence and severity of TMD is higher in women compared to men [1]. Results from a recent meta-analysis showed that women had a two-time higher risk in development of TMD [4]. In a clinical study of TMD patients, women showed significantly higher pain intensity on the VAS compared to men, as a respond to palpation of the masticatory muscles as well as the TMJ [5]. Results from the OPPERA study have shown that pain sensitivity, in the majority of all pain measurements, is significantly higher in women compared to men [45].

Because of the higher prevalence of TMD in women, we found it interesting to reveal gender differences in the serum analyses in both groups. The gender-matched serum analyses showed significantly higher levels of hemoglobin, cobalamin, PTH, and vitamin D, as well as significantly lower levels of creatine and potassium only in women in the TMD group, compared to the control group. Albumin levels were significantly higher in both men and women in the TMD group, and TSH was significantly higher only in men in the TMD patient group, compared to the control group. The results showed that most of the observed differences in serum analyses, for both groups, were in the subgroup of women. However, the observed gender differences may be affected by the fact that men were a very small population sample comprising only 9 subjects in each group. More research must be carried out to fully examine the possibility of an association between gender and serum levels in TMD.

The present study is one of the few studies on serum analyses in TMD patients comparing levels in healthy individuals. To our knowledge, this is the first study to use as many as 19 different variables at the same time. Despite a relatively small study sample, the results of our study may contribute toward assessing and mapping risk factors and characteristics of TMD. One limitation of the study was the fact that the serum samples were taken at all seasons of the year, while levels of some determinants, e.g., vitamin D and PTH, may have some seasonal variability in the Scandinavian countries. The fact that there was some geographical difference between the TMD patient group and the control group may also have had an effect on the results. The possibility of cultural, diet-related, and socioeconomic factors affecting serum levels of the presented determinants in our study, as well as other similar reports, should also be kept in mind. Another limitation is that ultrasound was not used for diagnostics of TMD, which has been tried but had too many obstacles to pass and therefore was not used. The gold standard for diagnostics of TMJ disease is magnetic resonance imaging (MRI) together with a clinical investigation for function and pain. However, ultrasound for diagnostics has recently been shown to be effective in the limb muscle and shoulders [46, 47].

5. Conclusion

In the present study, no clear indication of systemic disease or malnutrition in the TMD patient group was seen. The results from the serum analyses were mostly within normal reference values, which resulted in rejection of our hypothesis. All observed deficiencies in both groups were weak. One of the most surprising results was that vitamin D levels were lower in the control group compared to the TMD group. Despite minor observed differences in TMD patients, as compared with healthy subjects, we conclude that serum analyses should be not be used as a biomarker of TMD nor as a diagnostic tool for an individual subject with TMD. As an outcome from our clinical investigation, we observed a small group within the TMD group which likely took high doses of vitamin supplements, which contributed to elevated serum levels in some variables. Due to a relatively low number in the study population, more research is warranted to clarify the relationship between different serum determinants and the etiology and maintenance of TMD.

Data Availability

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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ORIGINAL RESEARCH

High Pain Intensity is a Risk Factor of Non-Resolving TMD: A Three-Year Follow-Up of a Patient Group in a Norwegian Interdisciplinary Evaluation Program

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Purpose: To investigate the outcome of patients with long-term refractory temporomandibular disorders (TMD) three years after a Norwegian interdisciplinary evaluation program with attention to patient satisfaction, function, pain, and psychosocial variables.

Patients and Methods: The study population consisted of 60 long-term refractory TMD patients who were investigated by a Norwegian interdisciplinary team. A questionnaire that covered medical history, function, pain, lifestyle factors, TMD-status and follow-up from their general medical practitioner (GMP) was sent to the patients three years after the evaluation. Questionnaires that assessed function (Mandibular Functional Index Questionnaire [MFIQ] and Roland Morrison Scale [RMS]), pain intensity (General Pain Intensity questionnaire [GPI]) and psychosocial factors (Hospital Anxiety and Depression scale [HADS]); a 2-item version of the Coping Strategies Questionnaire [CSQ]) were included in the package.

Results: Thirty-nine out of 60 TMD patients completed the questionnaires. Improvements in TMD symptoms were reported in 10 patients (26%), were unchanged in 16 patients (41%) and worsened in 13 patients (33%). Only 8 patients (21%) were satisfied with the follow-up of the suggested treatments from their GMP. Significant improvements of symptoms were noted in MFIQ (jaw function), GPI (including pain intensity at maximum and suffering from pain), and CSQ (pain related catastrophizing), in all 39 TMD patients as one group. However, a subgroup analysis showed that the significant improvements were mostly within patients who reported improvement of TMD symptoms. A high pain intensity at baseline was a significant risk factor *(OR = 5.*79, 95% CI: 1.34, 24.96) for patients who reported worsening of TMD symptoms at follow-up.

Conclusion: High pain intensity at baseline was a significant risk factor for poorer recovery three years after an interdisciplinary evaluation. Our data support the notion that improved coping with TMD pain includes both decreased pain intensity, CSQ and MFIQ scores.

Keywords: catastrophizing, interdisciplinary, orofacial pain, refractory pain, stress, evaluation

Introduction

Temporomandibular disorders (TMD) are characterized by pain and dysfunction of the temporomandibular joint (TMJ) and the masticatory apparatus.[1,2] The prevalence of TMD related signs and symptoms has been estimated to be approximately 30% in the general population,[3] predominantly in women.[4] The Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study has reported a 4% incidence per year of first onset of TMD.[1] TMD has been linked to many comorbidities including fibromyalgia, irritable bowel syndrome, and depression, additionally to trauma and stress symptoms.[1,5–9] Significantly higher prevalence of psychosocial factors such as somatic awareness, distress, catastrophizing, pain amplification, and psychosocial stress in subjects with TMD symptoms compared to healthy individuals, was observed in the OPPERA study.[1,10] Our group have previously reported increased saliva levels of stress hormones together with increased psychometric scoring, decreased pain thresholds and catastrophizing as predictors for TMD.[11,12]

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Several systematic reviews of TMD highlight the lack of evidence on how to base management decisions.[13–15] In 2013, the Norwegian Ministry of Health established a national interdisciplinary evaluation program for TMD patients at Haukeland University Hospital (HUH) in Bergen, Norway. The missions were to establish an assessment program consisting of several specialists who would characterize the patient group, and establish national guidelines for assessment and treatment of TMD.[16] Chronic oral and facial pain, including TMD has been determined to be multifactorial and therefore should be investigated and treated by an interdisciplinary team in order to arrive at the correct diagnoses and provide appropriate and tailored treatments for the patients.[17] It is preferable that medical specialists, psychologists, physiotherapists, and dental specialists are all included in the team and together assess and treat these patients[18] to avoid patients being referred from one specialist to another and further subjected to treatment previously tried by other disciplines. The goal of our approach is to evaluate the patient's condition from as many different perspectives as possible and come up with a treatment plan that can be followed up by the patient's GMP. Further, it is important to exclude other diseases, give the patient an explanation of why they are in pain as well as give them different strategies for managing their pain and ensuring the best possible quality of life.[16,18–20]

There are no agreed, standardized guidelines for outcome measures of chronic pain management in clinical trials, but it has earlier been suggested that such measures should incorporate at least some of the 6 proposed core domains;[1] pain;[2] physical functioning;[3] emotional functioning;[4] participant ratings of improvement and satisfaction with treatment;[5] symptoms and adverse events; and[6] participant disposition.[21,22]

The present study was a follow up of patients with long-term refractory TMD who had been evaluated at the interdisciplinary clinic at HUH for a minimum of three years. The overall objective was to identify risk factors of non-resolving TMD, which may indicate the need for earlier treatment of these patients. Further objectives were to assess patients TMD symptoms, physical function, and psychosocial variables, and patients' satisfaction with treatments proposed by the interdisciplinary team.

Materials and Methods

Study Design

The present study was a longitudinal self-assessed questionnaire-based study of a group of patients with long term refractory TMD symptoms who had been evaluated at the Haukeland University Hospital (HUS) in Bergen with a follow-up of 3 years.[16] In addition, patients' satisfaction with the suggested treatments and follow-up by their GMP was evaluated. Pain related symptoms and dysfunction (both general and TMD-related), general health status, psychosocial factors, previous treatment and medication, and the duration of pain and disease were included in the evaluation.

Ethics

Ethical approval was granted by the Regional Ethical Review Board Southeast (2015/930) for the first examination, and for the present study (2018/647), in accordance with the Helsinki Declaration (1964). A written informed consent was received from all subjects who participated in the study.

Participants

Our study population consisted of 60 TMD patients, all affected with long term refractory TMD symptoms. The patients were referred to the National TMD-project from all health regions in Norway, by their GMP during the years 2013–2015 for an assessment by the interdisciplinary team and were consecutively included in the study. The inclusion criteria were adults older than 18 years with long-term TMD-related pain assessed by their GMP. The study patients were diagnosed by the team in accordance with a beta version of the TMD guidelines from the Norwegian National Health Directorate that were published in 2016,[23] which are comparable to the diagnoses included in the Diagnostic Criteria for TMD (DC/TMD).[24] Exclusion criteria were non-TMD-related orofacial pain, drug dependency, psychiatric diagnoses, and unresolved economic disability claims.

Baseline Data (First Evaluation)

The first evaluation was performed by the interdisciplinary evaluation team at HUH. The patients had completed a comprehensive questionnaire about their symptoms prior to the clinical examination. The questionnaire covered pain and other symptoms, psychosocial factors, physical functioning, symptoms, and adverse events (eg, facial trauma). A four-item GPI was used to indicate the TMD patients' subjective experience of pain and the degree of suffering from pain using the NRS. The patients reported their:[1] pain intensity at its minimum,[2] pain intensity when it was at its maximum,[3] how much they suffered from the pain, and[4] the lowest pain intensity they could accept to live with. A 0–10 NRS was used, where 0 represents no pain at all, and 10 represents the worst imaginable pain.[25] Other questionnaires were the HADS,[26] a 2-item version of the CSQ[27] regarding pain catastrophizing, RMS[28] and a shortened version of MFIQ. The RMS consisted of 24 claims regarding physical disability caused by general pain. The MFIQ is a tool for measuring mandibular function.[29] The questionnaire was a shortened version and consisted of five claims regarding mandibular functional impairment related to speech, yawning, and chewing. Claims regarding work were excluded from the MFIQ due to possible bias, since a significant proportion of TMD patients were unemployed or disabled by chronic pain. The claims were rated from 0–4, where 0 was "no difficulties" and 4 "was impossible without help".

Six different specialists examined the patients in the interdisciplinary team, an oral and maxillofacial surgeon, a dental specialist in orofacial pain, a pain physician, a physiotherapist, a clinical psychologist, and a medical radiologist. At the final consultation, the results of the assessment were presented to the patient along with an explanation of why they are in pain followed by treatment suggestions which were discussed with the patients and their relatives. A questionnaire with seven questions about how satisfied they were with the evaluation was given to the patients. The patients were informed that the rating of the evaluation was anonymous. The seven questions were: 1) Did you expect that the cause of pain could be detected? 2) Were you well received by the team? 3) Do you find the team to be skilled professionals? 4) Did the team show you respect? 5) Did you get proper information about the condition you have? 6) Did you get adequate information about the condition you have? 7) Was the investigation as expected? They were asked to fill it in at home and send it back by mail. All questions were rated from 1–10, where 1 was "totally satisfied" and 10 was "completely dissatisfied".

The suggested treatment plan was reported to their GMP with a request of a follow up. A description of the interdisciplinary work up and a characterization of the patient group with severe TMD has previously been published.[11,12,16,30,31]

Three-Year Follow Up

Three years after the interdisciplinary evaluation, the patients received a comprehensive questionnaire by mail, similar to the questionnaire that they had filled in at the first evaluation with the addition of questions regarding their satisfaction with the follow-up by their GMP. Further, there were questions regarding the progression of their TMD symptoms (on a five-point scale, from much improved to much worse) and general health symptoms (on a three-point scale, from improved to worse), what kind of treatments they had received and the outcome of the treatments. If they did not answer the questionnaire, they were reminded by the first author via a telephone call.

Statistical Methods

All statistical analyses were performed in STATA version 16 (StataCorp, College Station, TX, USA). Data from the first evaluation, were considered as baseline values for comparison with follow up values in the statistical analyses. Mean, median, range, and standard deviation (*SD*) were calculated for continuous variables. A Wilcoxon matched test was performed for comparison of GPI, HADS, RMS, CSQ and MFIQ, between the first examination and the follow-up. For further statistical analyses, the patients were divided into three subgroups: 1 Improvement of TMD symptoms (Group 1), 2 No difference in TMD symptoms (Group 2), and 3 worsening of TMD symptoms (Group 3). A Kruskal Wallis test with a post hoc Dunn test was performed to calculate significant differences (alpha = 0.05) between the three subgroups at both baseline and follow-up. A Wilcoxon matched test was used to calculate the *p*-value of no difference within the three subgroups from baseline to follow-up. A logistic regression model with the two subgroups Group 1 (improvement of TMD symptoms) and Group 3 (worsening of TMD symptoms) as the dependent variable and multiple independent baseline variables was performed as well. Both the unadjusted model, and adjusted model with stepwise forward method were calculated. For the adjusted model, the probability of

enter (pe) was set to $p<0.2$, and the probability of removal (pr) was set at $p>0.4$. A Chi-squared test was performed to measure association between TMD symptoms and general health in the 3×3 Table 1.

Results

Baseline Registrations

Baseline characteristics of all patients (n=60), responders at the three year-follow up (n=39), and non-responders at follow-up (n=21) are presented in Table 2. The TMD diagnoses in the whole study group of 60 patients were myalgia (n = 22), arthralgia (n = 1), disc derangement (n = 2), and combinations (n = 35). All 60 patients completed the evaluation of the interdisciplinary investigation. In general, the patients were very satisfied with the evaluation. The distribution of data from the 60 TMD patients who responded at the follow up are presented in Figure 1.

Follow-Up Registrations

Of the 60 TMD patients who participated in the interdisciplinary investigation program, 39 patients answered the follow-up questionnaires. The baseline characteristics of the 39 responders compared to the 21 non-responders are shown in

Table 1 Drop-Out Analysis Between Responders and Non-Responders at the 3-Year Follow Up Study

	All Patients at Baseline	Responders 3-Year Follow Up	Non-Responders 3-Year Follow Up
n patients	60	39	21
Baseline values			
Sex ratio F:M	6:1	9:1	3:1*
Age years: mean (range)	45 (20–69)	47 (24–69)	40 (20–69)*
Pain duration in years: mean (range)	11 (1–40)	13 (1–40)	7 (2–18)*
Psychometric measures:			
HADS: mean (range)	13.1 (0–39)	12.3 (0–39)	14.(71–38)
CSQ: mean (range)	7.(12–12)	7.(42–12)	7.(01–12)
GPI maximum: mean (range)	8.(64–10)	8.(96–10)	7.6 (0–10)
GPI suffering: mean (range)	7.(92–10)	8.(06–10)	7.3 (0–10)

Notes: Responders at the follow up (n = 39) had significantly higher age, longer pain duration and a higher female representation compared to non-responders (n=21). *Alpha=0.05.
Abbreviations: CSQ, Coping Strategies Questionnaire; GPI, General Pain Intensity Questionnaire; HADS, Hospital Anxiety Depression Scale.

Table 2 Patient's Health Development (n=39)

	n	%
TMD related health		
Much Better	2	5.1
Better	8	20.5
Unchanged	16	41.0
Worse	11	28.2
Much Worse	2	5.1
General health		
Better	6	15.4
Unchanged	17	43.6
Worse	12	30.8
No Answer	4	10.3

Note: Numbers and percentages on development of TMD symptoms, and general health in the follow up period.
Abbreviations: n, number; TMD, temporomandibular disorder.

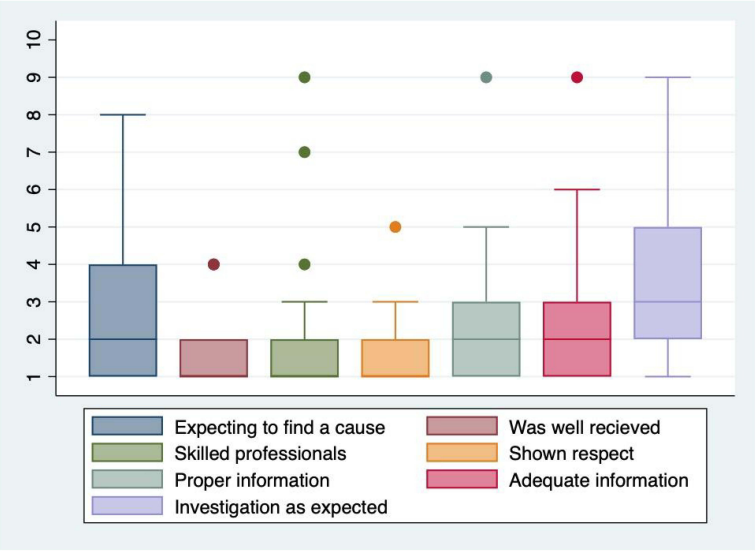

Figure 1 Rating of the interdisciplinary evaluation.
Notes: Results are from the patient's own evaluation after the interdisciplinary investigation of TMD patients at HUH (n=60). The evaluation consisted of seven questions regarding the patients' experience of the examination and evaluation process. Answers were rated from 1–10, where 1 was "totally satisfied" and 10 was "completely dissatisfied". The ratings were anonymous and could not be linked to the patients who were informed of this.
Abbreviations: HUH, Haukeland University Hospital in Bergen, Norway; TMD, temporomandibular disorder.

Table 2. There were some missing answers in the 39 completed questionnaires. The number of patients who filled in the questionnaires is specified in each table of the 39 patients at follow up, the initial diagnoses included myalgia (n = 11), arthralgia (n = 1), disc derangement (n = 2), and combinations (n = 25).

TMD Related Health and General Health

TMD symptoms were improved in 10 patients (26%), unchanged in 16 patients (41%), and worsened in 13 patients (33%) (Table 3). General health symptoms were improved in 6 patients (15%), unchanged in 17 patients (44%) and worsened in 12 patients (31%) (Table 3). The coincidence between TMD symptoms and general health at follow up is presented in Table 1.

Table 3 Coincidence Between TMD Symptoms and General Health (n=35)

General Health	Development of TMD Symptoms			Total
	Unchanged	Improved	Worse	
Unchanged	12	1	4	17
Improved	2	4	0	6
Worse	2	5	5	12
Total	16	10	9	35
p (Chi-squared):	**0.006**			

Notes: This Table represents the coincidence between TMD symptoms and general health at follow up. The count of 35 patients is due to the fact that 4 patients did not report general health, and all the 4 patients were within the group who reported worsening of TMD symptoms.
Abbreviations: n, number; TMD, temporomandibular disorder.

Pain Intensity and Suffering from Pain

Improvements in the maximum pain intensity (NRS 0–10) was reported at the follow-up (from NRS 9.0 to 8.0; $p<0.001$), and the highest level of suffering from pain decreased (median value from 8.0 to 7.0; $p<0.001$). No statistical differences were reported in the minimum pain ($p=0.38$), nor in the option of the highest pain intensity that the patients would accept to live with ($p=0.11$) (Figure 2A–D).

Functional Related Questionnaires

The MFIQ score was significantly lower at the follow-up compared to the baseline level (decrease in median value from 12.0 to 10.0; $p<0.001$). The RMS was not significantly changed ($p=0.218$) (Table 4).

Psychosocial-Related Questionnaires

The results from the CSQ significantly showed a lower score at the follow-up compared to the baseline level (decrease in median value from 8.0 to 6.5; $p=0.03$). No statistical differences were observed in HADS ($p=0.175$), anxiety ($p=0.33$), and depression ($p=0.32$) (Table 4).

Satisfaction of the Follow Up by Their GMP

Only 8 patients (21%) were satisfied with the follow-up by their GMP, while 15 patients (39%) were dissatisfied. Eleven patients (28%) were not sure, and three patients (8%) reported that their GMP did not follow-up at all. Two patients (5%) did not answer.

TMD Related Treatments and Outcome

Self-reported treatments of TMD are presented in Table 5 (n=39). The most frequently reported treatment was an occlusal splint (n=27, 69%). The second most frequent treatment was analgesics, reported by 24 patients (62%). The third most frequent treatments were physiotherapy and self-treatment/ exercises, both reported by 22 patients (56%). It should be noted that individual patients could have had several different treatments (Table 6).

Subgroup Analysis

In the group that reported worsening of TMD symptoms (Group 3), the maximum pain intensity was significant higher at baseline compared to the other groups (Table 7, time *a*). Furthermore, Group 3 had significant higher minimum pain

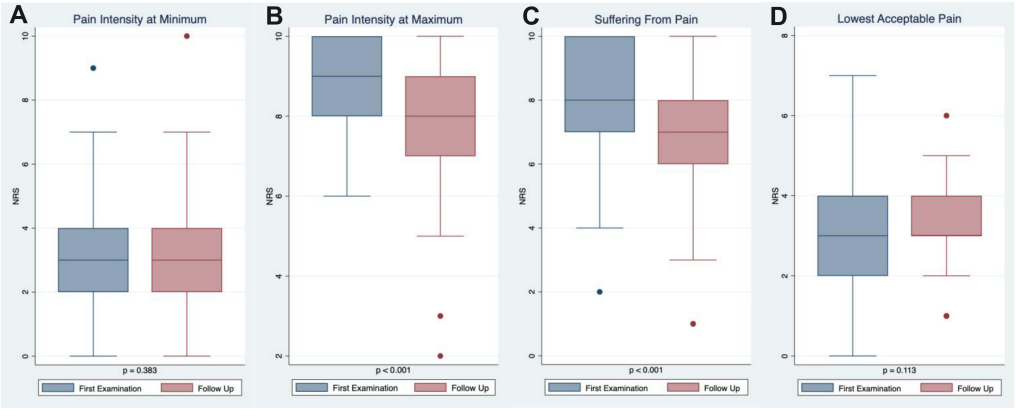

Figure 2 (**A–D**) General Pain Intensity and degree of suffering. Results from the GPI, using a NRS (0–10), where 0 refers to no pain, and 10 refers to the worst imaginable pain. Data are from the 39 patients who completed the questionnaire at the follow-up study. The results from the follow-up are compared to the first evaluation.
Abbreviations: GPI, General Pain Intensity Questionnaire; NRS, Numeric Rating Scale.

Table 4 Results from Psychosocial- and Functional Related Questionnaires

	Anxiety (0–21)	Depression (0–21)	HADS (0–42)	CSQ (0–12)	RMS (0–24)	MFIQ (0–24)
First examination						
Mean	6.9	5.3	12.3	7.4	7.4	12.6
Median	6.0	4.0	11.0	8.0	7.0	12.0
Range	0.0–20.0	0.0–19.0	0.0–39.0	2.0–12.0	1.0–21.0	2.0–22.0
SD	4.6	4.4	8.5	2.3	4.3	4.4
Follow-up						
Mean	6.3	4.8	11.0	6.3	6.8	9.7
Median	6.0	4.0	11.0	6.5	6.0	10
Range	0.0–20.0	0.0–18.0	0.0–38.0	0.0–12.0	0.0–21.0	0.0–20.0
SD	5.1	4.2	8.9	3.2	4.5	5.2
n patients	38	38	38	38	37	38
***p*-value** (Wilcoxon matched)	0.325	0.332	0.175	0.033	0.218	<0.001

Notes: Results from the questionnaires; HADS, CSQ, RMS, and the MFIQ. Higher scores refer to greater difficulties. The number of patients who completed the questionnaires are specified in the second last row. Most questionnaires were filled out by 38 out of 39 patients at both first examination and the follow-up, except RS which was filled out by 37 out of 39 patients. A Wilcoxon matched test was performed to calculate the *p*-value between the completed questionnaires at first examination (baseline), and at the follow-up study.
Abbreviations: CSQ, Coping Strategies Questionnaire regarding pain catastrophizing; HADS, Hospital Anxiety Depression Scale; MFIQ, Mandibular Function Index Questionnaire; n, number; *p*, probability; RMS, Roland Morris Scale; *SD*, standard deviation.

Table 5 Treatment of TMD in the Follow Up Period

	Treatment of TMD:		Positive Effect on TMD From Treatment:	
	(39 patients)		(21 out of 39 patients)	
	n	%	n	%
Analgesics (unspecific)	24	61.5	10	41.7
Antidepressants	6	15.4	0	0.0
Anxiolytics	5	12.8	3	60.0
Sleep drugs	8	20.5	2	25.0
Physiotherapy	22	56.4	7	31.8
Surgery	8	20.5	4	50.0
Psychologist	5	12.8	0	0.0
Dental Splint	27	69.2	9	33.3
Dental Treatment	6	15.4	0	0.0
Self-treatment/ Exercises	22	56.4	10	45.5

Notes: Data from the first columns ("Treatment of TMD") refers to the number and percent of patients (out of 39 patients) who reported treatment of TMD they had undergone during the follow-up period. The right column ("Positive effect on TMD from treatment") refers to the number of patients out of 39, who reported positive effects of the current treatment on their TMD. In total there were 21 patients who reported the positive effect of at least one treatment.
Abbreviation: TMD, temporomandibular disorder.

intensity, higher maximum pain intensity as well as higher level of suffering from pain, followed by Group 2>Group 1 (Table 7, time *b*). Further, Group 1 patients showed significantly lower minimum pain, maximum pain and suffering from pain at the follow up (Table 7).

No statistical differences were seen between the three subgroups at baseline analyzing HADS, CSQ, RMS, and MFIQ (Table 8, time *a*). But at the follow up, significantly lower (positive outcome) CSQ score in Group 1, and significantly higher (negative outcome) MFIQ in Group 3 were seen (Table 8, time *b*). Improvement in MFIQ scores was observed within Group 1 and 2 from baseline (time *a*) to the follow up (time *b*), while only the patients in Group 1 had a significant decrease in CSQ score (Table 8). A logistic regression model showed that high maximum pain intensity at baseline was a significant risk factor to reported worsening of TMD symptoms at follow-up (Table 9).

Table 6 Number of Several Different Treatments

Sum (n) Treatments	n Patients	%	Cumulative %
0	3	7.69	7.69
1	4	10.26	17.95
2	7	17.95	35.90
3	9	23.08	58.97
4	5	12.82	71.79
5	6	15.38	87.18
7	2	5.13	92.31
8	3	7.69	100.00
Total	**39**	**100**	

Note: This is in addition to Table 5 and shows how many patients received multiple treatments.
Abbreviations: n, number; TMD, temporomandibular disorder.

Discussion

This study presents a three-year follow-up of a group of patients with long term refractory TMD, with a mean of 13.4 years of pain, who were assessed by an interdisciplinary team in a National Norwegian program for TMD patients, on request from the Norwegian Health Directorate, a part of the Government. As a group, the TMD patients were satisfied with the interdisciplinary evaluation at baseline, but the majority of these patients were dissatisfied with the follow up by their GMP three years later, and only one third of the patients reported an improvement in their TMD symptoms at follow up. One third reported unchanged status and one third reported worsening of their TMD symptoms, where high pain intensity at baseline was considered as a risk factor. In those with a positive outcome, we observed statistically significant improvement in some measures, such as mandibular function, maximum pain intensity and pain related catastrophizing.

Long-term follow-up results of chronic TMD in the OPPERA study have been reported and an improvement of TMD was shown, including jaw function, pain pressure thresholds, psychosocial variables and somatic symptoms.[32] In our study, we also observed some improvements in functioning and psychosocial factors, even in those patients who reported their TMD symptoms unchanged. However, it is important to note that the patients in our study were long term refractory TMD (13.4 years), and our results may therefore differ from other studies.

Other factors may influence outcomes as it has been shown that physical and emotional functioning might affect the pain intensity over time.[21] The presence of several TMD-associated clinical findings, has been associated with a poorer treatment outcome compared to if there is only one finding.[33] Also, the number of other comorbidities is associated with higher pain intensity and duration in TMD.[34] Discrepancies between patient's subjective feeling and the clinician's objective evaluation are common and may explain differences between symptoms and clinical findings.[35]

There is evidence that interdisciplinary evaluations and treatments improve quality of life in chronic pain patients.[18] Several studies suggest the need for improvement in the interdisciplinary approach with the development of individual/tailored pain treatments as well including both dental and medical specialists in the interdisciplinary team.[17,18,36] Furthermore, the patients should not only be investigated by an interdisciplinary team, but they should also be treated by the disciplines recommended. It is also important to simultaneously manage psychological comorbidities to achieve the intended treatment outcome in patients with chronic orofacial pain.[17]

As shown in this study, the patients rated the interdisciplinary evaluation highly. Most of the patients resided in other parts of the country and were referred back to be treated at their place of residence. Since specialists are concentrated in cities in Norway there can be lack of specialist treatments and multidisciplinary teams in rural areas. It was assumed that the treatment suggestions from the interdisciplinary team would be followed up by the GMP but most of the patients were not satisfied with the follow up that they actually received, reflecting the situation that most patients did not get the opportunity to be treated in an interdisciplinary way. Other factors that may explain why most patients in the present study did not report improvement in their TMD symptoms might be that this patient group had long term refractory pain

Table 7 Subgroup Analysis of General Pain Intensity Using a NRS (0–10)

GPI (NRS 0–10) by Subgroups	Min Time *a*	Min Time *b*	Max Time *a*	Max Time *b*	Accept Time *a*	Accept Time *b*	Suffering Time *a*	Suffering Time *b*
Gr 1: Improvement of TMD								
n patients	10	10	10	10	10	10	10	10
Mean	3.4	2.0	8.3	5.8	2.4	2.7	7.6	4.4
Median	4.0	1.5	8.5	5.5	2.5	3.0	8.0	4.5
Range	1.0–6.0	0.0–5.0	6.0–10.0	2.0–9.0	1.0–4.0	1.0–4.0	4.0–10.0	1.0–7.0
SD	2.0	1.6	1.2	2.7	1.0	0.9	1.7	2.4
***p*-value time** (Wilcox. match.)	-	0.008	-	0.008	-	0.406	-	0.002
Gr 2: No change of TMD								
n patients	16	16	16	16	15	16	16	16
Mean	2.6	2.4	8.6	8.3	3.0	3.1	7.7	7.1
Median	2.0	2.5	9.0	8.0	3.0	3.0	8.0	7.0
Range	0.0–6.0	0.0–5.0	6.0–10.0	7.0–10.0	0.0–7.0	1.0–6.0	2.0–10.0	3.0–10.0
SD	1.6	1.3	1.3	1.0	1.8	1.3	2.1	1.7
***p*-value time** (Wilcox. match.)	-	0.766	-	0.375	-	0.918	-	0.064
Gr 3: Worsening of TMD								
n patients	13	13	13	13	13	12	13	13
Mean	3.9	5.1	9.6	9.2	3.2	3.8	8.7	8.3
Median	3.0	4.0	10.0	9.0	3.0	4.0	9.0	8.0
Range	2.0–9.0	2.0–10.0	8.0–10.0	7.0–10.0	1.0–6.0	1.0–5.0	5.0–10.0	6.0–10.0
SD	2.4	2.4	0.7	1.0	1.4	1.3	1.5	1.3
***p*-value time** (Wilcox. match.)	-	0.195	-	0.123	-	0.209	-	0.125
***p*-value subgroups** (Kruskal Wallis) (Post hoc Dunn test, alfa = 0.05)	0.331	0.002 (Gr 3 sign diff from Gr 1&2)	0.014 (Gr 3 sign diff from Gr 1&2)	0.003 (All Gr sign diff)	0.351	0.088	0.207	<0.001 (All Gr sign diff)

Notes: Data divided into subgroups of TMD patients who reported improvement of their TMD symptoms in the follow-up period (Gr 1, n=10), patient who reported no change in TMD symptoms (Gr 2, n= 16) and the TMD patients who reported worsening of TMD symptoms (Gr 3, n=13). Time *a* refers to baseline (first evaluation), and time *b* refers to follow up. The table presents results from the GPI, using a NRS (0–10). The number of patients who completed the questionnaires are specified under each variable. A Wilcoxon matched test was performed to calculate the *p*-value between baseline measurement (time *a*) and the follow-up (time *b*) within the subgroups. A Kruskal Wallis test was performed as a hypothesis-test between subgroups. Significant values (alpha = 0.05) were followed up by a post hoc Dunn test.

Abbreviations: Accept, the lowest pain intensity the patient would accept to live with; GPI, General Pain Intensity Questionnaire; Gr, group; Max, pain intensity at maximum; Min, pain intensity at minimum; n, number; NRS, Numeric Rating Scale; *p*, probability; *SD*, standard deviation; Suffer, suffering from pain.

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Table 8 Subgroup Analysis of Psychosocial- and Functional Related Questionnaires

	CSQ Time *a* (0–12)	CSQ Time *b* (0–12)	RMS Time *a* (0–24)	RMS Time *b* (0–24)	MFIQ Time *a* (0–24)	MFIQ Time *b* (0–24)	HADS Time *a* (0–42)	HADS Time *b* (0–42)
Gr 1: Improvement of TMD								
n patients	10	10	10	9	9	10	10	10
Mean	7.2	3.8	5.8	4.3	12.7	7.1	10.3	7.1
Median	7.5	3.0	4.5	4.0	13.0	6.5	10.5	4.0
Range	2.0–12.0	0.0–12.0	1.0–13.0	0.0–12.0	8.0–17.0	0.0–14.0	4.0–18.0	0.0–23.0
SD	2.5	3.3	3.8	3.4	3.0	4.4	4.9	7.5
***p*-value time** (Wilcox. matched)	-	0.004	-	0.469	-	0.004	-	0.082
Gr 2: No change of TMD								
n patients	16	16	16	16	16	16	16	16
Mean	6.9	6.8	7.9	7.6	10.9	8.9	13.8	12.8
Median	7.5	6.5	7.0	6.0	11.0	8.0	11.5	10.0
Range	2.0–10.0	2.0–11.0	2.0–21.0	2.0–21.0	2.0–19.0	1.0–18.0	0.0–39.0	0.0–38.0
SD	2.2	2.6	5.0	5.6	4.6	5.3	10.0	10.9
***p*-value time** (Wilcox. matched)	-	0.931	-	0.746	-	0.025	-	0.316
Gr 3: Worsening of TMD								
n patients	13	12	13	13	13	13	13	13
Mean	8.2	7.8	7.9	7.5	14.5	13.8	12.0	11.8
Median	8.0	8.0	8.0	7.0	14.0	11.5	11.0	12.0
Range	5.0–12.0	2.0–12.0	2.0–13.0	1.0–13.0	8.0–22.0	8.0–20.0	0.0–29.0	0.0–24.0
SD	2.4	2.6	3.9	3.2	4.5	4.0	8.8	6.2
***p*-value time** (Wilcox. matched)	-	0.680	-	0.544	-	0.102	-	0.620
***p*-value subgroups** (Kruskal Wallis) (Post hoc Dunn test, alfa= 0.05)	0.489	0.020 (Gr 1 sign diff from Gr 2&3)	0.429	0.066	0.163	0.020 (Gr 3 sign diff from Gr 1&2)	0.790	0.217

Notes: Data divided into subgroups of TMD patients who reported improvement of their TMD symptoms in the follow-up period (Gr 1, n=10), patients who reported no change in TMD symptoms (Gr 2, n= 16) and the TMD patients who reported worsening of TMD symptoms (Gr 3, n=13). Results from the questionnaires; HADS, CSQ, RMS, and the MFIQ are presented. Higher scores refer to greater difficulties. Time *a* refers to first evaluation (baseline), and time *b* refers to follow up. The number of patients who completed the questionnaires are specified under each variable. A Wilcoxon matched test was performed to calculate the *p*-value between baseline measurement (time *a*) and the follow-up (time *b*) within the subgroups. A Kruskal Wallis test was performed as a hypothesis-test between subgroups. Significant values (alpha = 0.05) were followed up by a post hoc Dunn test.

Abbreviations: CSQ, Coping Strategies Questionnaire regarding pain catastrophizing; Gr, group; HADS, Hospital Anxiety Depression Scale; MFIQ, Mandibular Function Index Questionnaire; n, number; *p*, probability; RMS, Roland Morris Scale; *SD*, standard deviation.

Table 9 Logistic Regression of Baseline Variables

Dependent Variable: TMD Symptoms at Follow-Up: Worse (Gr 3, n=13) vs Improved (Gr 1 n=10)				
Logistic regression: Unadjusted model				
Baseline variable	**Description**			**p:**
Age	Age at baseline (years)			0.53
Gender	Gender; female, male			0.42
HADS Score	HADS score at baseline (0–42)			0.57
CSQ Score	CSQ score at baseline (0–12)			0.32
RMS Score	Roland Morris Scale score at baseline (0–24)			0.20
MFIQ Score	MFIQ score at baseline (work excluded) (0–24)			0.28
GPI Minimum	GPI NRS (0–10) at baseline: Pain intensity when at minimum			0.56
GPI Maximum	GPI NRS (0–10) at baseline: Pain intensity when at maximum			0.02
GPI Acceptable	GPI NRS (0–10) at baseline: Lowest pain intensity to accept to live with			0.14
GPI Suffering	GPI NRS (0–10) baseline: Suffering from pain			0.14
Multivariable logistic regression: Adjusted stepwise, forward				
Worse/Improved	***OR***	***p***	**95% CI**	
GPI Maximum	5.79	0.018	1.34	24.96

Notes: Presentation of a logistic regression model with the two subgroups Gr 1 and Gr 3 as the dependent variable and multiple independent baseline variables. Both unadjusted model, and adjusted model with stepwise forward method were performed. Pain intensity at maximum was significantly associated with worsening of TMD symptoms.

Abbreviations: CI, confidence interval; CSQ, Coping Strategies Questionnaire regarding pain catastrophizing; GPI, General Pain Intensity Questionnaire; Gr, group; HADS, Hospital Anxiety Depression Scale; MFIQ, Mandibular Function Index Questionnaire; n, number; NRS, Numeric Rating Scale; *p*, probability; RMS, Roland Morris Scale; *SD*, standard deviation; TMD, temporomandibular disorder.

at their initial visit. A large longitudinal register study of chronic pain in Norway (HUNT Study) has shown that treatment of long-term chronic pain, especially in combination with psychosocial factors, has a poor prognosis.[35]

In this study the maximum pain or how much the patients suffered from pain was improved at follow-up, though the pain intensity was still high. In the subgroup analysis, among those who reported that the TMD symptoms had improved, lower pain intensities and less suffering from pain was reported. In the groups that reported that the TMD symptoms were unchanged or worse, pain intensities were not significantly different from baseline. Higher pain intensity has also been associated with poorer TMD prognosis in a previous longitudinal study,[37] as well as patients who experience pain more frequently have a poorer prognosis.[38] Adaptation to chronic pain has been supported by findings from long-term follow-up of TMD patients in the OPPERA study, where the pain intensity significantly decreased.[32] It seems that adaptation to pain is more common among those with lower pain intensity compared to those with higher pain intensity as was the case in this study. This is further supported by the results from the present study that the best predictor for reporting worsened TMD symptoms at follow up, was high pain intensity at baseline.

In this study, the TMD patients still had high scorings in CSQ and HADS at the follow-up, though the CSQ was statistically decreased compared to baseline. While the CSQ score was statistically equal in all subgroups at baseline, there was a significantly lower CSQ score among those who reported improvement at the follow-up. Chronic stress in patients with TMD has been considered an important characteristic of TMD, as previously shown by high CSQ and HADS scores.[11,12,39] Psychosocial factors, including stress, have also been considered as a major risk factor in TMD,[1,10,40] in the development of chronic pain.[41] Elevated CSQ may indicate poorer prognosis for pain relief in chronic pain in general.[41] Results from the OPPERA study have shown that pain catastrophizing may decrease in long term (median 7.6 years) follow-up of chronic TMD,[32] even without associations with subjective improvement of TMD. However, findings from the present study together with previous studies may indicate that improved coping with TMD includes both decreased pain intensity and CSQ scores.

In a large longitudinal study, longer duration of chronic pain and higher pain intensity were significantly associated with anxiety and depression disorders, suggesting that both pain and psychological disorders have a worsening impact on

each other.[42] Furthermore, psychosocial factors are considered important in the perception and tolerance of pain.[43] The experience of fear related to pain is individual and may increase pain intensity and anxiety in two ways;[44] where pain leads to avoidance of physical activity and the anxiety related to pain might increase the focus on pain and result in higher suffering.[45] Chronic pain and psychological symptoms such as anxiety and depression are commonly observed together and may reinforce each other and impair the prognosis for the improvement of chronic pain.[42,46] It has also been suggested that both pain and stress might modulate the same neurobiological pathways, which have a major effect on the outcome of their endocrinologic signals.[47–49] Results from a Randomized Controlled Trial (RCT), with one-year follow up, showed that patients who had been educated to self-treatment of TMD, reported significantly greater decrease of pain intensity, and increase in coping with pain, compared to patients who received TMD treatment by health professionals.[50] These results may indicate that it is important for the patient to take responsibility for their own recovery.

Recommended treatment of TMD includes jaw muscle exercises, relaxation exercises, and sometimes an occlusal splint or NSAIDs.[2,23,51,52] The authors of a recent RCT study have concluded that jaw motion exercises are a cost-effective and pain reducing treatment.[52] The most common treatments reported by patients in our study were conservative treatments, including jaw muscle exercises, occlusal splint, and physiotherapy. The fact that only 10 out of 39 patients reported improvement of TMD might be due to different circumstances including the fact that the GMP and not the general dentist had the responsibility for the follow up and treatment. The GMP does normally not treat TMD and the general dentist might lack knowledge of how to treat TMD. Treatment of severe TMD belongs to specialists, both within dentistry and medicine, who ideally should form interdisciplinary teams, however there is a shortage of specialists in rural parts of Norway.

Treatment of chronic pain is a challenge; available treatment options do not necessarily reduce pain intensity or improve psychological and functional variables in an effective manner.[53] However, during the last few decades there has been a switch in the scientific approach to chronic pain, from a direct linear association with tissue damage, to a multifactorial etiology including several biopsychosocial factors.[54] It has reasonably been suggested that psychosocial health care should be involved in treatment of chronic pain and the appropriate goal for the future should be individualized pain management program for each patient.[17,55]

Limitations to this study include the reliability and validity of the self-reported questionnaires. A previous study on the outcome of treatment for TMD reported a 44% discrepancy between the doctor's evaluation and the patients' answer to a TMJ symptom and function assessing questionnaire in which patients scored their symptoms both better and worse.[35] The Authors had no control over whether the patients followed up with their GMP, in accordance with the suggested treatment plan. The relatively small study population and low response rate, and the fact that the patients were not clinically examined at follow up should also be considered as a limitation. In the drop-out analysis, patients who responded at the three-year follow-up had a longer pain duration and slightly higher age at baseline compared to the non-responders (Table 1) suggesting that a possible selection bias might be that responders were more severely affected than non-responders.

Conclusion

This study of patients with long-termed refractory TMD, evaluated by a Norwegian Government sponsored interdisciplinary team showed that high pain intensity at baseline was a significant risk factor for poorer recovery after three years. Findings from the present study together with previous studies may indicate that improved coping with TMD pain includes both decreased pain intensity, CSQ and MFIQ scores. The authors want to encourage further research on management of stress in the presence of chronic pain as an important factor for treatment outcome. Furthermore, it is important to improve access to trained care in rural areas and to maintain the interdisciplinary process. If the Interdisciplinary team were to follow up with the patients and the GMP/general dentist, the results of the treatment could be improved. To further increase the quality of care, a personalized, digital rehabilitation program with feedback could be established, which could give the patient the opportunity to take responsibility for their own recovery.

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Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL RESEARCH

Kordian Staniszewski et al.

Neurocognitive Functioning in Patients with Painful Temporomandibular Disorders

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Abstract:

Aim: To investigate psychosocial factors in painful TMD (pTMD) which could have consequences for mastering chronic pain.

Methods: Our study included 22 patients (20 women, 2 men) with pTMD, refractory to conservative treatment, and 19 healthy controls. The control group was matched for gender, age, and educational level, and IQ tested on the Wechsler Abbreviated Scale of Intelligence. Neurocognitive function was tested with the Color-Word Interference Test (CWIT). Pain intensity was reported according to the General Pain Intensity Questionnaire (GPI), using the Numeric Rating Scale (NRS). Self-perceived cognitive difficulties were reported by the Perceived Deficits Questionnaire-Depression 5-item (PDQ-5**)**. Two measures of rumination were included: the Rumination-Reflection Questionnaire (RRQ) and the Ruminative Response Scale (RRS). The Montgomery Åsberg Depression Rating Scale Self-report (MADRS-S) was used to measure depressive symptoms, and the Oral Health Impact Profile-TMD (OHIP-TMD) to measure QoL related to oral health.

Results: There were no statistical differences in age (median pTMD: 55 years, median control: 53 years), educational level, and IQ between pTMD and controls. Median pain intensity in pTMD was NRS 8 at maximum and the median pain duration was 18 years. There were no significant differences in CWIT between pTMD and controls. Self-perceived cognitive function (PDQ) was significantly poorer in pTMD. Rumination scores from both measures, and the depression score from MADRS, were significantly higher in pTMD. The OHIP-TMD score revealed a significantly poorer QoL in pTMD.

Conclusion: The group of pTMD patients have self-perceived cognitive difficulties that may make it more difficult to master chronic pain and common everyday tasks. They reported significantly more self-perceived cognitive difficulties, higher rumination, more depressive symptoms, and lower QoL compared to healthy controls, suggesting that these psychosocial factors could be targeted in treatment and interventions. However, the tested neurocognitive performance was equivalent to the control group.

Keywords: Cognitive Function, Chronic Pain, Self-perceived Deficits, Depressive Symptoms, Rumination, Quality of Life.

Introduction

Temporomandibular disorders (TMD) are conditions that can cause pain, discomfort, and functional difficulties in the temporomandibular joint and the muscles involved in chewing (1). TMD have been found to be associated with several other comorbidities, including fibromyalgia, irritable bowel syndrome, and depression, and additionally to trauma and stress symptoms (2) In the OPPERA study, it was found that individuals with TMD symptoms were more likely to have higher prevalence of psychosocial factors such as somatic awareness, distress, catastrophizing, pain amplification, and psychosocial stress, when compared to healthy individuals. (3, 4). Several studies have strongly associated catastrophizing, anxiety, and depression with TMD (5, 6), and one study observed a significant correlation between catastrophizing and higher pain intensity in a group of patients with temporomandibular joint disorders and chronic pain (7). Previous research has demonstrated a higher likelihood of TMD in patients with a history of specific mental health and behavioral disorder diagnoses (8).

TMD patients make high demands of the healthcare system in terms of resources and finances, due to experienced non-resolving pain, sick leave, and disability (9). Based on the outcome from a review of chronic pain, it has been suggested that the patient's emotional state may have a significant effect on how pain is experienced, through modulation of neuroendocrine and peripheral factors (10). Despite this link between chronic pain and cognitive processes and their impact, few studies have investigated the relationship between pain and neurocognitive function.

Neurocognitive function is a complex theoretical concept which can be divided into three main domains comprising memory, executive function, and attention. There are several aspects within each domain (11). Executive function (EF) is defined as the neurocognitive processes that regulate behavior, affects, and thoughts (12). One aspect of EF is cognitive inhibition, which can be measured by the Stroop effect (13), and is defined as "The stopping or overriding of a mental process, in whole or in part, with or without intention" (14-16). The Stroop test assesses this effect as the ability to inhibit/stop an automated skill (specifically reading) and is a measure of prepotent response inhibition, which is the ability to deliberately suppress dominant responses. Cognitive functioning, including EF, can also be assessed by self-reported measures, but most studies find small correlations between standardized tests and self-reported measures (17). Both these aspects of cognition contribute to

everyday functioning, and therefore both the Stroop task and self-reported cognition EF might be useful when conducting studies of neurocognitive functioning in patients with TMD.

As far as we know, few studies have investigated associations between EF and chronic pain outside more general conditions such as fibromyalgia (18), and only one of these focused on TMD patients (19). This study of 17 female TMD patients and matched controls reported a slower cognitive rate and longer response times for a cognitive inhibition task in the TMD group (19). A meta-analysis suggested that there were small to medium differences between chronic pain patients and neurocognitive inhibition (18). In populations of patients with fibromyalgia, neurocognitive testing has given contraindicatory results, however. More research of cognitive functioning in chronic pain patients is thus needed to investigate the extent to which neurocognitive deficits contribute to functioning, symptoms, and quality of life.

Self-reported complaints have also previously been reported to be associated with the increased severity of chronic pain, including self-perceived cognitive deficits (20), quality of life (QoL) related to oral health (21, 22), and rumination (23, 24). Rumination is an emotional regulation strategy consisting of repetitive negative thoughts about past events and aspects of oneself, and is associated with anxiety, depression, and neurocognitive deficits (25). Ruminative processes could potentially exacerbate pain (23), and can be separated into reflective depressive and brooding rumination, of which the former is the least pathological (26). Depressive rumination (26) is associated with low mood and could mediate the association between pain and depression. Pain could induce a lowered mood, causing depressive rumination. Neurotic rumination is the tendency to ruminate more independently of sad mood (27), which could be important with regard to chronic pain, as it represents a general tendency for maladaptive emotional regulation processes (24). However, little is known about the presence of these emotional regulation strategies in groups with chronic pain. Rumination would be expected to be higher in connection with chronic pain and associated with depressive states, lowered mood, and lower QoL.

The overall aim of the present study was to investigate psychosocial factors in painful TMD (pTMD) that could have consequences for the mastering of chronic pain. The psychosocial factors, including

neurocognitive function, self-perceived cognitive difficulties, rumination, depression and QoL, were compared to healthy controls. We hypothesized that: 1) Cognitive inhibition measured by the Stroop test is significantly poorer in patients with pTMD compared to controls; and 2) Self-reported cognitive function and QoL is poorer, and rumination and depression is higher, in pTMD patients compared to controls.

Methods

Study design

The present study utilized a controlled cross-sectional design to compare patients with pTMD to a healthy control group. The patients in the present study were previously assessed as part of a national interdisciplinary evaluation program for program for pTMD at Haukeland University Hospital (HUH) in Bergen, Norway (28).

Study population

The pTMD patients were referred by their GMP to the National TMD project from all health regions in Norway during the years 2013-2018, for assessment by the interdisciplinary team, and were consecutively included in the study. The patients with pTMD were referred to the National TMD project by GMP from various health regions in Norway between 2013 and 2018. These patients underwent assessment by the interdisciplinary team and were consecutively included in the study. The inclusion criteria were adults older than 18 years with long-term TMD-related pain. The patients included were diagnosed by the interdisciplinary team in accordance with a beta version of the TMD guidelines from the Norwegian National Health Directorate that were later published in 2016 (29), which are comparable with the diagnosis included in the Diagnostic Criteria for TMD (DC/TMD) (30). Exclusion criteria were non-TMD-related orofacial pain, substance abuse, obvious psychiatric diagnoses, and unresolved economic disability claims. In total, 129 pTMD patients were clinically examined.

During 2021, the pTMD patients were invited by email to participate in the present study. Exclusion criteria for the TMD patients in the present study were the same as for the interdisciplinary investigation, in addition to (color) blindness, poor Norwegian language skills, and IQ< 70. A control group was randomly selected using the Norwegian National Population Register (*Folkeregisteret*) and invited by email to join the project, and also by recruiting acquaintances of the research group. In total,

150 control subjects were invited via the Norwegian National Population Register. The control group was matched with the pTMD patients in terms of age, gender, and educational level. The control group were adults matched by age and gender with the pTMD patient group. Exclusion criteria for controls were TMD symptoms or other musculoskeletal pain, and symptoms in the head and neck area, (color) blindness, poor Norwegian language skills, and IQ< 70.

Ethics

Ethical approval was granted by the Regional Ethical Review Board Southeast (2015/930) for the first 60 TMD patients, and (2018/647) for an extension to 129 patients, in accordance with the Helsinki Declaration (1964). The present study was a continuation of previous research from the interdisciplinary evaluation program at HUH. Written informed consent was received from all subjects prior to testing, and participating in the study.

Educational level

The educational level of each subject was registered and categorized in 6 levels: 1) primary school, 2) vocational diploma, 3) high school, 4) bachelor's degree, 5) master's degree, 6) PhD or higher.

Assessment of general cognitive functioning

To assess whether the subjects' general intelligence differed, the 2-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI) was performed for both the TMD patients and the healthy controls. The test consisted of a vocabulary and a matrix reasoning task (31). This was performed in order to evaluate whether differences between the groups in the Color-Word Interference Test (CWIT), and other outcomes, were due to specific deficits in inhibition or differences in general cognitive functioning (IQ)

Neurocognitive inhibition test/Stroop test

The neurocognitive testing of the TMD patients and control subjects was performed at the Neuropsychological Clinic at the Faculty of Psychology, University of Bergen. The test applied was the CWIT from the Delis-Kaplan Executive Functioning Scale, consisting of four subtests to evaluate processing speed, inhibition, and mental flexibility, (32). The subtests include S1) naming colors, S2) reading colors, S3) inhibition, and S4) switching. Subtest 3 consists of naming colored words, where there is a mismatch between the name of a color (e.g. "blue", "green", or "red") and the color it is

printed in (e.g. the word “red” printed in blue ink, instead of red ink). The test subject is asked to name the color of the print, and not the incongruently written word, resulting in an inhibition of the automatic tendency to read (Stroop effect). In subtest 4, the subject alternates between reading color words and naming the color printed in a mismatching ink (S2 and S3 switching). A test score was registered for each subject, based on the time in seconds the subject needed to perform each subtest, and the number of errors for each subtest. Two additional CWIT measurements were calculated; 1) Contrast inhibition = S3-((S1+S2)/2) and 2) Contrast switching = S4-((S1+S2)/2).

Questionnaires

Subjects in the pTMD and control groups were asked to fill in personal information, including age, gender, and educational level. Several validated questionnaires were included in the study for self-administration by the subjects.

A four-item General Pain Intensity Questionnaire (GPI) was used to indicate the subjects’ subjective experience of pain and degree of suffering from pain, according to the Numeric Rating Scale (NRS). The subjects reported their: 1) pain intensity when it is at a minimum, 2) pain intensity when it is at a maximum, 3) how much they suffered from pain, and 4) the highest pain intensity they could accept to live with. A 0-10 NRS was used, where 0 represents no pain at all, and 10 represents the worst imaginable pain (33).

Both the Rumination-Reflection Questionnaire (RRQ) (27) and the Rumination Response Scale (RRS) (26) were included. The RRQ is a 24-item questionnaire based on a 1-5 scale, where 1 represents “strongly disagree” and 5 represents “strongly agree” to statements on the tendency to ruminate or reflect on various aspects of self-related thought. The first 12-point rumination scale (RRQ questions 1-12) consists of questions concerning negative self-referential thought associated with neuroticism (Trapnell & Campbell, 1999). The second 12-point rumination scale (RRQ questions 13-24) measures reflection. The RRS is a 22-item 4-point scale measuring depressive rumination from 1-“almost never” to 4-“almost always” (range 22-88).

The Montgomery Åsberg Depression Rating Scale Self-report (MADRS-S) (34) is a 9-item questionnaire measuring depressive symptoms during the past three days. MADRS-S is based on a 7-point scale (0-6) to evaluate the state of depression, where a higher score refers to a higher level of depression symptoms.

For brief assessment of self-perceived cognitive difficulties, the Perceived Deficits Questionnaire-Depression 5-item (PDQ-5**)** (35) was used. The PDQ-5 is a five-item, 5-scale (0-4) questionnaire, where a higher score refers to greater difficulties.

The Oral Health Impact Profile (OHIP) is a reliable and validated measure of QoL related to oral health (36). OHIP is based on a numeric 0-4 scale, where 0 represents “never” and 4 represents “very often”. OHIP-TMD was the version administrated by the subjects in the present study. OHIP-TMD is a 22-item questionnaire that has previously been reported to be an appropriate psychosocial measure of QoL in patients with TMD (37).

Statistical analyses

All statistical analyses were performed in STATA (StataCorp, College Station, TX, USA v.17). Mean, median, range, and standard deviation (SD) were calculated for each variable in both study groups. A p-value of no difference between the pTMD group and the control group was calculated with a Wilcoxon rank-sum test (Mann-Whitney U test) for all variables, except pain duration due to non-applicable data in the control group.

Results

Study population

In total, 126 of the 129 pTMD patients from the National pTMD project at HUH received an invitation to participate in the study. 39 out of the 126 pTMD patients signed up to participate in the study. 22 out of 39 pTMD patients completed the tests in the present study. In the control group, 11 out of 19 subjects were tested and included by random selection from the Norwegian National Population Register. The remainder of the control subjects were recruited from among acquaintances and co-workers at the university who were not part of the research group in the present study. The final study group consisted of 20 women and 2 men in the pTMD group, and 17 women and 2 men in the control group. Further details of the study population included are presented in Figure 1.

Insert figure 1 approximately here

Demographic data

There were no statistical differences in age, educational level, and IQ between the pTMD group and the control group. Demographic data is presented in Table 1.

Insert Table 1 approximately here

TMD diagnoses and pain intensity

The TMD diagnoses for the full study group of 22 pTMD patients were myalgia (n = 10), arthralgia (n = 2), disc derangement (n = 3), and combinations (n = 7). The median pain intensity for the pTMD group was NRS 8 at maximum and NRS 3 at minimum. The median suffering from pain was reported to be NRS 5 out of 10. Only one control subject reported pain (not in the head and neck area). The median highest intensity of pain with which the subjects could accept to live was significantly higher for the pTMD group than for the control group. Details of pain intensity are presented in Table 2.

Insert table 2 approximately here

Neurocognitive inhibition

There were no statistical differences in CWIT performance between the pTMD group and the control group (Table 3).

Insert table 3 approximately here

Questionnaires

Rumination scores from RRQ questions 1-12, and the RRS, were significantly higher for the pTMD group. The depression score from MADRS was also significantly higher for the pTMD group. Self-perceived cognitive function, shown by tPDQ, was significantly poorer for the pTMD group. The score from the OHIP-TMD revealed a significantly poorer QoL related to oral health in the pTMD group. There were no differences in reflection scores from the RRQ. Details of results from the questionnaires are presented in Table 4.

Insert table 4 approximately here

Discussion

In the present study, we observed that pTMD patients reported higher pain intensity, more self-reported cognitive difficulties, depression, low oral-health related quality of life (QoL), and more rumination (not reflection) compared to the control group. However, neurocognitive inhibition measured by a Stroop test did not differ significantly between the pTMD group and the control group.

Hypothesis 1) regarding group differences in neurocognitive inhibition measured by the Stroop test was not supported. The authors of a small, previous study of TMD patients, using similar measures of inhibition, observed a slower response to all Stroop tasks compared to a control group (19). This could suggest a more general deficit in processing speed, rather than a specific deficit in inhibition in TMD patients. However, none of the CWIT conditions measuring processing speed differed in the present study, contrary to this notion. There are few studies of TMD in relation to cognitive inhibition. However, several studies of patients with fibromyalgia and general chronic pain have investigated the relationship between chronic pain and impaired cognitive function. Similar to our results, one study of fibromyalgia patients reported subjective patient complaints, while cognitive inhibition examined by errors on a Stroop task did not differ from a healthy control group (38). In another study, patients with fibromyalgia showed poorer attention, but not inhibition, compared to a control group (39). On the other hand, results from a Stroop test have shown slower cognitive processing in patients with fibromyalgia compared to healthy subjects (40). Better cognitive inhibition shown by Stroop interference score has also been associated with lower pain intensity in healthy subjects (41). Similarly, poorer cognitive inhibition was observed in patients with high-intensity chronic pain, compared to healthy individuals (42). The conclusion from a meta-analytic review was that there were significant deficits in cognitive inhibition in populations with chronic pain, although the risk of bias is high (18). In the present study, the results of no significant difference in cognitive inhibition in pTMD compared to the control group might be due to a small sample size and selection bias, as the recruitment rate to participate in our study was low. Future studies of neurocognitive deficits in EF and inhibition in pTMD should therefore use sensitive measures and be adequately powered to detect small to medium effects.

Hypothesis 2) regarding group differences in self-reported cognitive functioning, depression, QoL, and rumination was supported. The pTMD patients reported significantly poorer cognitive function, higher depression, rumination, and reduced quality of life (QoL) related to oral health, compared to the healthy controls. The fact that neurocognitive inhibition measured by the Stroop task did not differ from the control group indicates that mastering of chronic pain and everyday tasks is more related to self-perceived cognitive deficits, rather than neurocognitive function measured by behavioral/neuropsychological tests. Patients experience more cognitive impairments than they show in task performance. The results are similar to a study of patients with chronic idiopathic pain, where self-perceived cognitive deficits, pain-related disability, and reduced QoL were observed, compared to a healthy control group (20). It thus seems that patients with chronic pain and pain-related disabilities suffer from self-perceived cognitive deficits and depression, even when executive function measured by neurocognitive tests is similar to healthy individuals. There could be several reasons for this, as previously discussed by Friedman and Gustavson (17). Self-reported cognitive functioning is more sensitive to certain deficits than neurocognitive tests, the latter often being administered in highly controlled, stationary environments. Subjectively reported cognitive functioning could thus be more ecologically valid, since it measures how patients actually function in their everyday life (17). This could be particularly relevant for chronic pain patients who might not be disrupted by pain in stationary tasks, such as neuropsychological testing, but might experience increasing difficulties and distress when out and about in their everyday lives. This was supported by a previous study that found an interaction between gait movement and Stroop performance in a population with chronic back pain (43). In conclusion, self-reported cognitive deficits are more apparent in pTMD than objective deficits, they could influence everyday functioning, and interventions reducing such deficits should be developed. In addition, future studies of pTMD should utilize more extensive cognitive self-reported measures to assess which areas of cognitive functioning (e.g. memory/EF) are most affected.

The group of pTMD patients in the present study reported significantly higher depressive (RRS) and neurotic (RRQ questions 13-24) rumination. Notably, reflection (RRQ questions 13-24) as an adaptive form of rumination did not differ from the control group. Rumination could potentially exacerbate pain (23), disrupt cognitive functioning and predispose individuals for depression, anxiety, and insomnia (25), and contribute to relapse and recurrence of depression (44). Neurotic rumination could influence

sensitivity to negative emotion, and has been associated with a more severe course of illness in depression (45), and as likely to contribute to the relatively high levels of depression in the pTMD group. Importantly, the groups did not differ in reflection, supporting the presence of pathological emotional regulation in this group. In sum, the current findings support significantly pronounced dysfunctional emotional regulation strategies in pTMD patients compared to controls, which represents a risk factor for psychiatric disorders. Interventions targeting pathological rumination, such as cognitive behavioral therapy and mindfulness interventions, could be useful to prevent exacerbation of pain and the development of psychiatric disorders, and should be considered for pTMD patients.

Results from the OHIP-TMD questionnaire in the present study revealed that oral health-related QoL was significantly poorer in the pTMD group compared to the control group. Poorer oral health-related QoL has also been related to more severe TMD in a previous study (21). In another study, oral health-related QoL was also significantly lower in TMD patients compared to a control group, and significantly correlated with higher pain intensity in the TMD group (22). Findings indicate that the severity and pain intensity in TMD are correlated with poorer QoL.

The study had several considerable strengths. A well-selected pTMD sample underwent comprehensive cognitive assessment, including neurocognitive tests, emotional regulation, depression and pain, controlled by an IQ measure. To the authors' knowledge this is one of the most comprehensive assessments of cognitive functioning in chronic pain patients in general and pTMD patients in particular. The groups were matched according to age and gender and did not differ in terms of important demographical variables. In addition, random sampling through recruitment under the Norwegian National Population Register was implemented. The internal validity and comprehensive assessments came at the cost of external validity and statistical power.
The limitation of the present study is, as mentioned, the small sample size, and possibly selection bias. The recruitment rate was low for both the pTMD group and the control group, and it is reasonable to assume that individuals with poor cognitive skills would seek to avoid participating in the study, as they might feel that they did not perform well enough in such tasks. A lack of significant results from neurocognitive tests could be due to a type-II error due to the small sample size.

Altogether, it seems that patients with pTMD might suffer from self-perceived cognitive deficits, rumination, and depressive symptoms, which would probably make it even harder for them to handle their pain and could put them at risk of exacerbation and developing psychiatric disorders. It is possible that patients with pTMD could increase their cognitive functioning by completing a cognitive training program to increase QoL. Such interventions have previously shown significant results for the cognitive functioning of patients with lowered mood and major depression (46), and potential long-term improvements in self-reported EF (47). In patients with chronic myofascial pain, self-care interventions have been shown to reduce pain intensity, and increase QoL (48). Nowadays, such interventions can be developed through digital platforms, with professional treatment feedback for patients.

Conclusion

Our results show that pTMD patients have self-perceived cognitive difficulties which may make it more difficult to master chronic pain and common everyday tasks. However, the neurocognitive inhibition tested by CWIT did not significantly differ from the control group. Based on our results, the hypothesis of “Neurocognitive inhibition is poorer in pTMD” was rejected, and the hypothesis “Self-perceived cognitive function and QoL is poorer, and rumination and depression are higher in pTMD” was approved, and the latter might put patients at risk of functional and psychological exacerbation. To improve pTMD treatment outcomes, a learning and mastering course in orofacial pain and digital treatment feedback was recently launched at HUH. To further increase the quality of care and the opportunity for patients to take responsibility for their own recovery, cognitive training and psychoeducation via digital platforms are being developed, and future studies should assess how those influence cognitive function and QoL.

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Disclosure

The authors report no conflicts of interest in this work.

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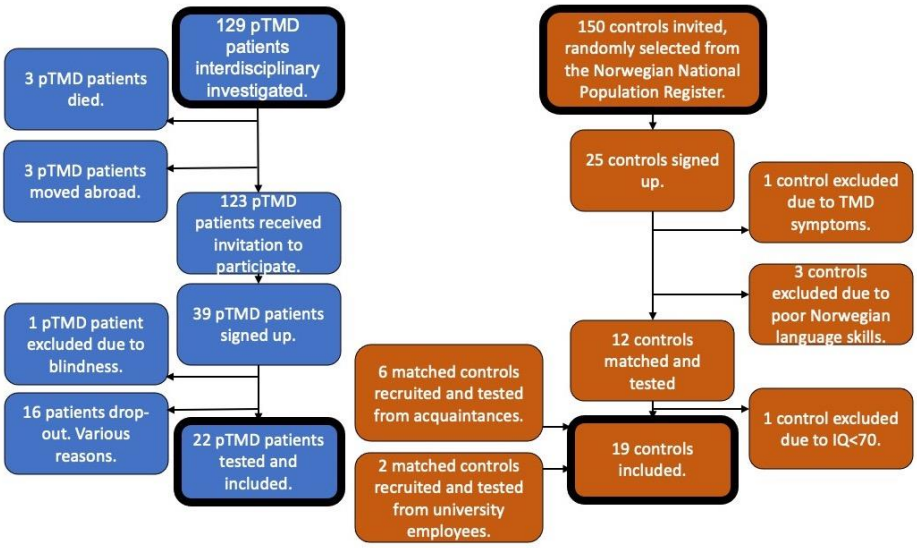
Figure Legends

Figure 1 Flow chart of pTMD patients and healthy individuals included
Note: In total, 22 pTMD patients and 19 controls were tested and included in the study.
Abbreviations: TMD, temporomandibular disorder; pTMD, painful temporomandibular disorder.

Figure 1 Flow chart of pTMD patients and healthy individuals included



Note: In total, 22 pTMD patients and 19 controls were tested and included in the study.
Abbreviations: TMD, temporomandibular disorder; pTMD, painful temporomandibular disorder.

Table 1 Demographic data of pTMD patients and controls

Demographics	**Age** (Years)	**Education** (Level 1-6)	**WASI** (IQ)	**Pain duration** (Years)
pTMD (n=22; 20W, 2M)				
Mean	54	3.1	112	21
Median	55	3.5	115	18
Range	34-78	1-5	94-130	7-42
SD	11.5	1.4	10.8	10.1
Control (n=19; 17W, 2M)				
Mean	53	3.5	118	Na
Median	56	4	117	Na
Range	33-78	1-5	107-134	Na
SD	11.0	1.2	6.4	Na
***p*-value** (Wilcoxon exact)	0.995	0.441	0.161	Na

Note: There were no statistical differences in age, educational level, or IQ between the pTMD group and the control group.
Abbreviations: M, men; n, number; pTMD, painful temporomandibular disorders; SD, standard deviation; W, women.

Table 2 General Pain Intensity Questionnaire using the Numeric Rating Scale

General Pain Intensity	**GPI Min** (NRS 0-10)	**GPI Max** (NRS 0-10)	**GPI Suffer** (NRS 0-10)	**GPI Accept** (NRS 0-10)
pTMD (n=22; 20W, 2M)				
Mean	2.5	7.5	5.6	3.1
Median	3.0	8.0	5.0	3.0
Range	0-7	4-10	1-10	0-5
SD	1.9	1.8	2.6	1.3
Control (n=19; 17W, 2M)				
Mean	0.2	0.5	0.4	1.6
Median	0.0	0.0	0.0	2.0
Range	0-4	0-10	0-8	0-7
SD	2.3	2.3	1.8	1.9
***p*-value** (Wilcoxon exact)	<0.001	<0.001	<0.001	0.002

Note: Results from the GPI questionnaire, using the NRS (0-10). All variables were significantly higher for the pTMD group compared to the control group, including pain intensity at minimum, pain intensity at maximum, how much the subjects suffered pain, and the highest pain intensity the subjects could accept to live with.
Abbreviations: GPI, General Pain Intensity; M, men; NRS, Numeric Rating Scale; n, number; pTMD, painful temporomandibular disorders; SD, standard deviation; W, women.

Table 3 Neurocognitive performance tested with the Color Word Interference Test (CWIT)

	S1 Naming colors (Sec)	**S2 Reading** (Sec)	**S3 Inhibition** (Sec)	**S4 Switching** (Sec)	**Contrast inhibition** S3-((S1+S2)/2)	**Contrast switching** S4-((S1+S2)/2)
TMD (n=22; 20W, 2M)						
Mean	34.7	25.9	67.3	82.7	37.0	52.4
Median	33.0	24.0	58.5	72.0	29.8	39.0
Range	24-60	16.0-55.0	39.0-187.0	46.0-276.0	14.5-129.5	21.5-218.5
SD	10.0	8.4	30.5	47.8	23.7	41.5
Control (n=19; 17W, 2M)						
Mean	33.5	24.4	56.6	72.6	27.6	43.6
Median	34.0	24.0	55.0	71.0	27.5	42.0
Range	21.0-48.0	18.0-39.0	44.0-87.0	54.0-111.0	18.5-49.5	25.0-79.0
SD	7.6	5.3	9.6	15.8	7.1	13.4
***p*-value** (Wilcoxon exact)	1.000	0.790	0.200	0.964	0.113	0.974

Note: Results from the CWIT, based on the Stroop effect. All variables were statistically equal between the pTMD group and the control group. Presented results are in seconds for S1, S2, S3 and S4. Additionally, two variables were calculated, including contrast inhibition (contrast S3), and contrast switching (contrast S4).
Abbreviations: CWIT, Color Word Interference Test; GPI, General Pain Intensity; M, men; n, number; pTMD, painful temporomandibular disorders; S, subtest; SD, standard deviation; Sec, seconds; W, women.

Table 4 Results from psychosocially-related questionnaires

Questionnaires	**RRQ 1-12** (Score 12-60)	**RRQ 13-24** (Score 12-60)	**RRS** (Score 22-88)	**MADRS** (0-54)	**PDQ** (Score 5-20)	**OHIP TMD** (Score 0-88)
TMD (n=22; 20W, 2M)						
Mean	35.3	35.8	35.6	9.7	12.5	43.9
Median	36.0	35.0	33.5	8.0	12.0	43.0
Range	20-48	27-57	23-50	2-27	8-19	17-67
SD	7.5	7.2	8.0	6.1	2.9	13.5
Control (n=19; 17W, 2M)						
Mean	27.1	33.7	30.4	4.0	8.5	5.2
Median	27.0	32.0	27.0	3.0	9.0	1.0
Range	12-43	22-45	22-53	0-15	5-15	0-36
SD	8.5	7.1	8.9	3.9	2.5	9.0
***p*-value** (Wilcoxon exact)	0.003	0.564	0.021	<0.001	<0.001	<0.001

Note: Results from the psychosocially-related questionnaires. All variables were significantly higher in the pTMD group compared to the control group, except RRQ questions 13-24 regarding reflection. The elevated scores in the pTMD group include rumination, depression, self-perceived cognitive deficits and quality of life related to oral health.
Abbreviations: M, men; MADRS, Montgomery Åsberg Depression Rating Scale; n, number; OHIP, Oral Health Impact Profile, pTMD, painful temporomandibular disorders; PDQ, Perceived Deficits Questionnaire; RRQ, Rumination Reflection Questionnaire; RRS, Rumination Response Scale; SD, standard deviation; W, women.

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