Toward Patient – Centric Evidence Generation and Synthesis in TMD/TMJ: Patient Round Table and Beyond

Danica Marinac-Dabic, MD, PhD, FISPE Director, Division of Epidemiology, CDRH/FDA
Outline

• TMD/TMJ - as a public health issue
• Context: Ongoing and evolving initiatives
  • MDEpiNet
  • CRNs
  • NEST
• Patient-Led Round Table - Progress to Date
• Key Gaps
• Promising Efforts and Opportunities
TMD

- Affects 35 million people (12%)
- Prevalence greater in women
- Complex disorder
- Gaps in evidence
- Need for interdisciplinary approach
Narrowing the Gap Between Currently Available and Urgently Needed

- Enhanced susceptibility and modifying factors (*e.g.*, sex):
  - Variability in clinical manifestation and disease severity
  - Variability in treatment responses and outcomes

- The need for diagnostic and prognostic biomarkers:
  - Intention-to-Treat population with [degenerative and ankylosis TMD](#) conditions to be treated with TMJ replacement
  - Predictive assessment of real-world device performance
  - Prevention and diagnostic/therapeutic management of adverse events

- *In silico* research and evidence integration for developing TMD-related Precision/Stratified Medicine applications
Assessment of Temp Dysfunction in Patients

Chronic Skull Joint Disease and Lactic Acidosis

Mark A. Dobler, Victor M. Rozental

1. Anesthesiology Research Laboratory, Thomas Jefferson Hospital, Philadelphia, PA
2. Medical Student, Thomas Jefferson University, Philadelphia, PA
3. Assistant Professor, Thomas Jefferson University, Philadelphia, PA
4. Resident, Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA

Correspondence should be addressed to Victor M. Rozental, MD, MS, Anesthesiology Research Laboratory, Thomas Jefferson University, 2030 Chestnut Street, Philadelphia, PA 19107.

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Association Between Symptoms of Posttraumatic Stress Disorder and Signs of Temporomandibular Disorders in the General Population

Stefan Kindler, MD; Christian Schwahn, PhD; Olaf Bernhardt, DDS; Andreas Söthof, DDS; Marija Mikoud, DDS; Reiner Bittar, DDS; Georg Meyer, DDS; Henry Völzke, MD; Hans Robert Metelmenn, MD; Hans Jürgen Grabe

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Aims: To estimate the association between signs of temporomandibular disorders (TMD) and symptoms of posttraumatic stress disorder (PTSD) in a representative sample from the general population of northeastern Germany. Methods: Signs of TMD were assessed with a clinical examination that included palpation of the temporomandibular joint (TMJ) and mastoidic muscles. PTSD was assessed with the PTSD module of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. The change-in-estimate method for binary logistic regression models was used to determine the final model and control for confounders. Results: After the exclusion of subjects without pretraumatic events, the sample for joint pain consisted of 1,673 participants with a median age of 58.9 years (interquartile range 24.8), and the sample for muscle pain consisted of 1,589 participants with a median age of 59.1 years (interquartile range 24.8). Of these samples, 84 participants had pain on palpation of the TMJ, and 42 participants had pain on palpation of the mastoidic muscles. Subjects having clinical PTSD (n = 62) had a 2.56-fold increase in joint pain (odds ratio [OR] = 2.56, 95% confidence interval [CI] = 1.14 to 5.71, P = .022) and a 3.86-fold increase (OR = 3.86, 95% CI = 1.51 to 9.75, P = .005) in muscle pain compared to subjects having no clinical PTSD.

Conclusion: These results should encourage general practitioners and dentists to acknowledge the role of PTSD and traumatic events in the diagnosis and therapy of TMD, especially in a period of international migration and military foreign assignments.
Systemic diseases, pain, and disorders: the temporomandibular joint and migraine

Abstract

Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are frequently associated with systemic diseases, pain, and disorders such as migraine. This study aimed to investigate the relationship between TMDs and other pain conditions, including migraine, in a population of 282 individuals. Participants were recruited according to the presence or absence of TMD and headache. The study found a significant association between TMD and migraine, with a higher prevalence of migraine in individuals with TMD compared to those without.

Keywords: Migraine, Headache, Temporomandibular joint disorder

Abstract

Relationship between Expanded Disability Status Scale scores and the presence of temporomandibular disorders in patients with multiple sclerosis

Lucas Sena Corrêa Carvalho, Osvaldo José Moreira Nascimento, Luciane Lacerda Franco Rocha Rodrigues, Andre Palma da Cunha Matta

Aims: To evaluate the prevalence of temporomandibular disorders (TMDs) in patients with relapsing-remitting multiple sclerosis (MS) and to investigate whether an association exists between the presence of TMD symptoms and the degree of MS-related disability.

Methods: 112 patients with MS were enrolled in the study. TMD symptoms were assessed using the Revised Temporomandibular Disorders (RDC/TMD) criteria. Disability was measured using the Expanded Disability Status Scale (EDSS).

Results: The prevalence of TMD symptoms was 46.4% in the MS group and 36.7% in the control group (P = 0.007). There was a significant correlation between the degree of MS-related disability and the presence of TMD symptoms (P = 0.028).

Conclusions: The presence of both TMD symptoms and MS-related disability was significantly greater in the MS group. EDSS scores and TMD prevalence rates were inversely related.

Keywords: Multiple sclerosis, Orofacial pain, Temporomandibular disorder
Association Between Chronic Tension-Type Headache Coexistent with Chronic Temporomandibular Disorder Pain and Limitations in Physical and Emotional Functioning: A Case-Control Study

Massimo Corsolini, Daniela Di Venere, France

1. MD, DMD, Assistant professor, Dental School University of Bari, Italy
2. DDS, PhD, PG Orth Assistant professor, Dental School Lucca
3. DDS, Assistant professor, Dental School University of Bari, Italy
4. DDS, Assistant professor, Dental School University of Milan, Italy
5. DDS, PhD, PG Oral Surg. Assistant professor, Dental School Poznan, Poland

Felix Bertram
Dental Student
Department of Prosthodontics
Philips University Marburg, Germany

Dagmar Schnabl, MD, DMD
Consultant
Department of Restorative and Prosthetic Dentistry
Medical University of Innsbruck, Austria

Rüdiger Emshoff, MD, DMD
Associate Professor
Department of Oral and Maxillofacial Surgery
Medical University of Innsbruck, Innsbruck, Austria

Iris Emshoff, MD
Resident
Department of Anaesthesia and Intensive Care Medicine
Medical University of Innsbruck, Innsbruck, Austria

Correspondence to:
Dr. Rüdiger Emshoff
University Clinic of Oral and Maxillofacial Surgery
Medical University of Innsbruck
Anichstraße 35
A-5020 Innsbruck, Austria
Tel: +43 5051334110 Fax: +43 5051334110

Aims: To assess the association between chronic tension-type headache coexistent with chronic temporomandibular disorder (TMD) pain and severe limitations in physical and emotional functioning. Sample size estimation was used to determine that this case-control study should include 126 subjects. Subjects suffering from chronic TMD who were aged between 18 and 68 were recruited in routine clinical practice. Of the 126 included subjects, 63 had TMD pain associated with chronic tension-type headache (cases) and 63 had TMD pain without a history of tension-type headache (controls). Clinical diagnosis of TMD was made according to the Research Diagnostic Criteria for TMD (RDC/TMD) Axis I criteria, and clinical diagnosis of headache was made according to the International Classification of Headache Disorders (ICHD-II). RDC/TMD Axis II criteria were applied to record the scores from the Graded Chronic Pain Scale (GCPS) and the Symptoms Checklist-90-Revised Depression (SCL-90) and Somatization (SCL-SOM) scales. A logistic regression analysis was used to assess the relationship between TMD pain with chronic tension-type headache and high levels of depression and somatization severity as scored on the SCL-90 and SCL-SOM scales, respectively, and high pain-related disability (GCPS grade III or IV). Data were adjusted to take into account age, gender, time since TMD pain onset, chronic TMD pain intensity, and characteristic pain intensity.

Results: The presence of chronic tension-type headache was significantly associated with severe SCL-90 (odds ratio [OR] = 7.2; P < .001), severe SCL-SOM (OR = 13.6; P < .001), and high pain-related disability (OR = 9.7; P < .001).

Conclusion: This study provides evidence of associations between the clinical diagnosis of chronic tension-type headache coexistent with chronic TMD pain and key aspects of physical and emotional functioning reflected in severe depression, severe somatization, and high pain-related disability. Oral Facial Pain Headache 2017;31:55–60. doi: 10.11607/opfh.1654
Conclusions

These findings imply that TMDs, chronic diseases, and ophthalmologic and otolaryngologic disorders hold various correlations, suggesting the need for multtarget approaches to effectively address this phenomenon.

CONCLUSION

IBS patients had a more than three times greater risk of TMD compared to HC. The risk of having TMD that also fulfilled criteria for TMD seem to share along with chronic facial and abdominal pain a significant co-occurrence with psychiatric disorders and female preponderance.
Impact in oral health of temporomandibular disorder in Parkinson’s disease


Nove de Julho University, Brazil

Abstract: [Purpose] The aim was to evaluate the prevalence of temporomandibular disorder (TMD) in a group of patients with Parkinson’s disease and to identify the factors associated with the disease. [Methods] A total of 30 patients with Parkinson’s disease were included in the study. The patients were divided into two groups: group A (PD-TMD) with at least one symptom of TMD and group B (PD) without any TMD symptoms. The presence of TMD was assessed by a standardized questionnaire. [Results] The prevalence of TMD was significantly higher in group A compared to group B (p < 0.05). Logistic regression analysis revealed that the presence of TMD was associated with bruxism (OR = 2.3, 95% CI: 1.02-5.2, p = 0.04) and lower jaw pain (OR = 2.8, 95% CI: 1.2-6.2, p = 0.02). [Conclusion] The prevalence of TMD in patients with Parkinson’s disease was higher than in the general population. The presence of TMD was associated with bruxism and lower jaw pain. Further studies are needed to explore the potential mechanisms underlying this association.

Pain threshold, sleep quality and anxiety levels in individuals with temporomandibular disorders


Abstract: [Purpose] The purpose of this study was to evaluate the pain threshold, sleep quality, and anxiety levels in individuals with temporomandibular disorders (TMD) and healthy controls. [Methods] A total of 30 participants with TMD and 30 healthy controls were included in the study. The pain threshold was assessed using a thermal pain test. Sleep quality was evaluated using the Pittsburgh Sleep Quality Inventory (PSQI). Anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI). [Results] The pain threshold was significantly higher in the TMD group compared to the control group (p < 0.05). The PSQI scores were higher in the TMD group compared to the control group (p < 0.05). The STAI scores were higher in the TMD group compared to the control group (p < 0.05). [Conclusion] Individuals with TMD have a higher pain threshold, lower sleep quality, and higher anxiety levels compared to healthy controls. These results suggest that TMD is associated with decreased pain sensitivity and increased anxiety. Further studies are needed to explore the potential mechanisms underlying these findings.
Prevalence of temporomandibular disorders in patients with Hashimoto thyroiditis

Abstract

Autoimmune thyroid disease (AITD), also known as Hashimoto thyroiditis (HT), is a degenerative inflammatory disease with high prevalence among women and has been associated with fibromyalgia and widespread chronic pain. The goal was to determine the frequency of temporomandibular disorders (TMD) in patients with HT.

Objectives

The aim of this systematic review was to evaluate the prevalence of tinnitus in patients with temporomandibular disorders (TMD) and the possible effects of TMD treatment on tinnitus symptoms. A search of the PubMed, Web of Science, and Cochrane databases from inception of each database up to January 2017 found 222 articles. After independent screening of abstracts by two of the authors, we assessed 46 articles in full text. The inclusion and exclusion criteria reduced these to 25 articles of which 22 studies reported prevalence based on 13,358 patients and 33,876 controls, and eight studies reported effect of TMD treatment on tinnitus based on 536 patients and 18 controls. The prevalence of tinnitus in patients with TMD varied from 3.7% to 70% (median 42.3%) whereas the prevalence in control groups without TMD varied between 1.7% and 26% (median 12%). The eight treatment studies, indicated that treatment of TMD symptoms may have a beneficial effect on severity of tinnitus. However, only one treatment study included a control group, meaning that the overall level of evidence is low. The finding that tinnitus is more common in patients with TMD means that it can be regarded as a comorbidity to TMD. However, in view of the lack of evidence currently available, further well-designed and randomized studies with control groups are needed to investigate whether possible mechanisms common to tinnitus and TMD do exist and whether TMD treatment can be justified to try to alleviate tinnitus in patients with TMD and comorbidity of tinnitus.

Results

A significantly elevated prevalence of TMD was found in patients with HT. Thus, patients with TMD who do not respond to therapy should be referred for thyroid diagnostic workup.

Conclusions

The two groups did not differ in terms of demographic parameters or mandibular jaw mobility. Significantly higher levels of anti-TPO and anti-Tg were attested in all subjects of the HT group. Markedly elevated prevalence of TMD was found in the HT group. Muscle pain and stiffness were found in 45 (86.5%) subjects of the HT group (p < 0.001), of whom 33 (63.4%) also had disc displacement with reposition (p < 0.001). Whereas 50% of the control group showed no TMD symptoms, all subjects in the HT group had symptoms.
Grounded in Epidemiology, Evidence Based Medicine and Health Services Research

- Outcomes Research (1986)
- Pharmacoeconomics (1989)
- Comparative Effectiveness Research (2003, 2009)
- Coverage with Evidence Development (2006)
- CRN-Community of Practice (2018)
Building Global Real World Evidence Collaboratives for Health Technologies

The Medical Device Epidemiology Network (MDEpiNet) is a global public-private partnership that seeks to advance the collection and use of real-world data to improve patient outcomes. MDEpiNet brings together stakeholders from across the health ecosystem to develop and improve real-world data infrastructure, and carry out studies to better understand how devices perform in the real-world.

MDEpiNet has taken a lead on the development of Coordinated Registry Networks (CRNs) as set out in the National Registry Taskforce (read JAMA Perspective below). The list of the currently developing CRN is listed in the box on this page below...
MDEpiNet: Intersections with FDA Strategic Initiatives and NEST
MDRTF Recommendations to FDA for NEST

Strategically Coordinated Registry Networks (CRN)

Principles:

- Link complementary sustainable registries/e-repositories (Professional society registries, EHRs, Claims data, PCORI-CDRNs)
- TPLC approach as a true continuum leveraging “real world” evidence
- “Dual purpose” existing national, regional or other large scale efforts
TMJ Patient-Led Round Table: Objectives

• Develop standardized data infrastructure: TMJ - CRN
• Affect a change in clinical trial practices to incorporate patient preference data and RWE experiences
• Develop a roadmap for the development of predictive analytics algorithms
• Develop evidence-based protocols and best practices for inclusion into health care
• Promote the development of collaborative multi-disciplinary research
TMJ Patient-Led Round Table Working Groups

• WG1. Natural History and Assessment of Biomarkers Associated with Outcomes in TMJ Implant Patients
• WG2. Patient Reported Outcomes Evaluation
• WG3. Physician and Patient Education, Patient-Centered Treatment
• WG4. Data Collection and Analysis
National TMD/TMJ Research Plan Domains

- Population/Epidemiologic Science
- Human Studies/Clinical Studies
- Basic Biological Science
- Data Science/Informatics
  - Example: In silico-approaches
 promise for advancing our understanding of the genetic contributions ..., risk factors for susceptibility and prognosis, and the development of individualized dental [and craniofacial] medicine.

- However, we are still in the early stages of the translation of genomics to clinic [and regulatory] practice.

Contributions of molecular genetic approaches to the study of oral and craniofacial diseases
TMD in Coremine knowledgebase:
>10,400 connections, including ~400 genes/proteins
Example of potential sex/race-related variability in utility of TMD biomarkers (Xiao et al 2015; 1000 Genomes)
A SNP in PTGS1 (rs3842803) showed the strongest association with global psychological symptoms. However, as this SNP is very rare in Caucasians/Europeans, but fairly common in African populations, the SNP remained strongly associated only in African-Americans.
Degenerative and ankylosis TMDs as indications for TMJ REPLACEMENT TMJ OA

TMDs (eg, chronic pain – nociceptive, neuropathic, etc.)
Ingenuity Knowledgebase (1): Genes involved in abnormal TMJ morphology

abnormal morphology of temporomandibular joint

INGENUITY®
Ingenuity Knowledgebase (2): genes that are associated with Abnormal TMJ Morphology and Osteoarthritis can be also involved in Neurological Functions.
In silico Framework: for Integrating Epidemiological and Genetic Evidence

Discovery of Biomarkers and Risk Predictors Based on In Silico Generated Epi-Gen Evidence

EPIDEMIOLOGICAL EVIDENCE from different sources (eg, RCT, EHR, registries)

GENETIC EVIDENCE from open-source and other available ‘omic databases (eg, NCBI/GEO)
In silico research: going beyond conventional evidence integration

- Apply Systems Biology/Medicine approach
- Integrate multidisciplinary evidence
- Extract new information by reanalyzing raw pre-existing data
- Integrate amassed device/biomaterial-related knowledge (e.g., biomedical, clinical, epidemiological, population genetics, etc)
- Promote translational research by incorporating pre-clinical findings
- Data analysis and interpretation using computer modeling and simulation:
  - Elicit and test new hypotheses
  - Cross-validate the results from different sources

Data repurposing and reutilization: the gift that keeps on giving
Biological and clinical plausibility of TMD study endpoints and biomarkers based on:
- Better understanding of molecular/mechanistic underpinnings
- Improved pre-selection for further qualification, validation and implementation steps

Clinical and regulatory relevance:
- New targets for different types of TMDs
- Well-categorized TMD biomarkers (e.g., diagnostic, monitoring, predictive, prognostic, etc)
- Well-defined target subpopulations (e.g., ITT for TMJ Replacement)
- Proactive surveillance using new study endpoints (e.g., biomarkers) for early detection and monitoring of adverse (clinical and subclinical) events in TMD/TMJ arthroplasty
- Less burdensome and more ethical - *in vitro* and *ex vivo* – TMJ device/biomaterial testing

Cost/time-efficient solutions for TMD-related Precision Medicine applications
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THANK YOU!

danica.marinac-dabic@fda.hhs.gov