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**CLINICAL-PHYSIOLOGICAL INDICES IN THE
MASTICATORY MUSCLE DYSFUNCTION**

323.01 - Stomatology

Summary of Doctor of Medical Sciences Thesis

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CONTENT

1. THE CONCEPTUAL CHARACTERISTICS OF THE RESEARCH	4
2. MATERIAL AND RESEARCH METHODS	6
2.1. General characteristics, study design, inclusion/exclusion criteria	6
2.2. Clinical examination (DC/TMD Protocol/Additional indices to the protocol)	7
2.3. Mathematical-statistical processing	9
3. THE PARTICULARITIES OF THE CLINICAL MANIFESTATIONS OF THE MASTICATORY MUSCLE DYSFUNCTION	9
3.1. The structure of the disease symptomatology (DC/TMD protocol) depending on the clinical variant/phase of the disease	10
3.2. The structure of the disease symptomatology (additional indices to DC/TMD) depending on the clinical variant/phase of the disease.....	11
3.3. Manifestation patterns of masticatory muscle dysfunction (cluster analysis)	15
4. EXTENSION OF DISORDERS ASSOCIATED WITH MASTICATORY MUSCLE DYSFUNCTION	18
4.1. Extent of pain in patients with masticatory muscle dysfunction	18
4.2. Indices of sensory function in different clinical subtypes of masticatory muscle dysfunction	20
4.3. Clinical subtypes of masticatory muscle dysfunction and psycho-emotional stress (DC/TMD Axis II/additional psycho-emotional indices)	23
GENERAL CONCLUSIONS	26
PRACTICAL RECOMMENDATIONS	26
REFERENCES (SELECTIVE)	27
LIST OF SCIENTIFIC PUBLICATIONS	28
ANNOTATION (Romanian, Russian, English)	33
LIST OF ABBREVIATIONS	36

1. THE CONCEPTUAL CHARACTERISTICS OF THE RESEARCH

The actuality of the subject. Temporomandibular disorders (TMD) are a collective term used for conditions characterized by pain and/or dysfunction of the masticatory muscles and/or the temporomandibular joint [1]. TMD have a significant economic impact – more frequent visits to medical service providers (on average 8.3 ± 9.0 visits/6 months); high costs of medical care (in the USA – \$4 billion annually) [2], significant impact on work capacity (annual losses of 17.8 million work-days/100 million people), as well as decrease in work quality (on average 12% decrease in productivity) [3]. Based on WHO data, TMD is the most common non-dental orofacial pain, the second most common musculoskeletal condition, and the third most common dental pathology [2]. In the general population, the prevalence of clinical forms of TMD is estimated to be between 7-31%, with the highest frequency of TMD occurring in women and in the 20-40 years age group [4].

Masticatory muscle dysfunctions remain an unsolved issue in terms of diagnosis and therapy, because it is based on multiple etiologies and multiple pathogenetic mechanisms, which interact in various ways, depending on the association of psychological disorders and the generalization of clinical manifestations. Currently, masticatory muscle dysfunctions are also approached within the concept of central sensitization, which opens up new possibilities in the diagnosis and interpretation of the etiopathogenesis of disorders in this category of patients. Some signs and symptoms may resolve spontaneously even without any intervention, while others may persist for years despite all management options being exhausted. Although for the standardization of the diagnostic process, the use of the DC/TMD protocol is currently recommended, the variety of clinical manifestations of the masticatory muscle dysfunctions requires the completion of diagnostic procedures both in the aspect of differentiating the clinical forms as well as taking into account the aspect of generalization and individualization. In the clinical approach to masticatory muscle dysfunctions, extensive and optimal criteria for diagnosing and monitoring the pathology have not yet been developed, attesting to a slow translation of scientific evidence into the clinical practice.

Working hypothesis. The personalization of the diagnosis of the clinical subtypes of masticatory muscle dysfunction can be achieved based on supplementing the DC/TMD protocol with local, regional and systemic clinical-physiological indices.

The aim of the study: Studying the particularities of masticatory muscle dysfunctions (clinical subtype, disease phase) based on the DC/TMD protocol supplementation with local, regional and systemic clinical-physiological indices.

Research objectives.

1. Studying the activity of the stomatognathic system in patients with masticatory muscle dysfunctions according to the phase of the disease (acute/chronic) and the clinical subtype (myogenous/myogenous-arthrogenous).
2. To identify based on the mathematical-statistical analysis (dimensionality reduction – feature selection, clustering) the distinct patterns of masticatory muscle dysfunctions based on the local, regional, systemic clinical-physiological indices and the potential therapeutic impact on the occlusal splints during the functional rehabilitation of the stomatognathic system.
3. Studying the particularities of generalized disorders (psycho-emotional state, sensory functions, fibromyalginess phenomenon) within the clinical subtypes of masticatory muscle dysfunctions.
4. Study of masticatory performance based on subjective and objective indices (two-color chewing gum test) in different clinical subtypes of masticatory muscle dysfunctions.
5. Development of integrative parameters for the assessment of pain manifestations in the stomatognathic system in patients with masticatory muscle dysfunctions.

Scientific research methodology. The research methodology was focused on modern concepts [6]: The biopsychosocial concept of interpreting masticatory muscle dysfunctions (DC/TMD protocol – Diagnostic Criteria for Temporomandibular Disorders); the concept of central sensitization syndrome (CSS

– central sensitization syndrome) of interpretation for the masticatory muscle dysfunctions and the expression of fibromyalginess phenomenon (polysymptomatic distress) in pain syndromes; the concept of stress in the etiology and pathogenesis of masticatory muscle dysfunctions; the methodology for evaluating muscle pain sensitivity in masticatory muscle dysfunctions (pressure pain threshold mapping); the methodology of subjective and objective evaluation of the masticatory function depending on the irregularities of the stomatognathic system.

Scientific novelty and originality:

1. For the first time, there were identified the indices of the activity of the stomatognathic system, that are statistically significantly associated with the clinical subtypes for masticatory muscle dysfunctions (myogenous/myogenous-arthrogenous; acute/chronic phase of the disease) and indices that are common to both criteria.
2. For the first time, based on the mathematical-statistical analysis, the clinical manifestations were identified, which differentiate patients with masticatory muscle dysfunctions into 2 distinct patterns (regional, regional-generalized) based on the extent and severity of the disorders.
3. The structure and severity of quantitative and qualitative indices of masticatory muscle dysfunctions depend on the expression of the fibromyalginess phenomenon (pain extent and related disorders).
4. The assessment of masticatory function requires the simultaneous assessment of and subjective indices, which describe different aspects of masticatory performance in patients with masticatory muscle dysfunctions.
5. For the first time, it was demonstrated that sensory hypersensitivity is an informative criterion, characteristic for the clinical subtypes of masticatory muscle dysfunctions.
6. For the first time, there was proposed a method for masseter muscle pain mapping with the assessment of the relative heterogeneity index of the pain map, which allows a new and informative approach to describing the masticatory muscle dysfunctions.
7. For the first time, it was demonstrated that experimental modeling of operational stress allows highlighting the change in pain tolerance and endurance of the masseter muscle, which in relative comfort conditions does not change essentially in patients with masticatory muscle dysfunctions, a fact that highlights certain particularities of the stress connection with the local manifestations of pain.

Practical importance:

1. The structure of the clinical picture and the expression of clinical-physiological indices of masticatory muscle dysfunction depends on the clinical variant (myogenous/myogenous-arthrogenous), the phase of the disease (acute/chronic) and the presence of generalization of symptoms (fibromyalginess phenomenon).
2. In the polymorphism of the stomatognathic manifestations of masticatory muscle dysfunctions, 4 groups of clinical features were highlighted: a) characteristic for the clinical subtype (myogenous/myogenous-arthrogenous); b) characteristic for the phase of the disease (acute/chronic); c) significant changes in different clinical subtypes and phases of the disease; d) no change according to clinical subtype & disease phase.
3. Differentiated evaluation of the masticatory function can be achieved through subjective and objective indices when applying the mixing ability test (two-color chewing gum test) in patients with dysfunctions of the masticatory muscles
4. Personalization of the diagnosis of masticatory muscle dysfunctions according to clinical subtypes can be made based on the sensory hypersensitivity indices.
5. There is a diagnostic value of experimental modeling the operational stress for its impact on quantitative-sensory indices in patients with masticatory muscle dysfunctions.
6. For the first time, there was developed a loco-regional pain examination technology, by analyzing the heterogeneity of the spatial distribution of mechanical pain sensitivity of the masseter muscle.

Implementation of scientific results. The results of the scientific research were implemented in the research, methodological and clinical activity at the Fala Dental Clinic, Megalux Dent Clinic, MI Municipal Dental Center, in the educational process at the Department of Therapeutic Dentistry of State University of Medicine and Pharmacy "Nicolae Testemițanu". **Approval of scientific results.** The results were presented through 27 active participations in national and international scientific forums, including: Anniversary Days of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (2017, Chisinau, Republic of Moldova; 2020, Chisinau, Republic of Moldova); VieSID Summer School Conference (2022, Vienna, Austria); MedEspera International Medical Congress (2020, Chisinau, Republic of Moldova); VII Congress of Neurologists (2021, Chisinau, Republic of Moldova); XXI International UNAS Congress (2017, Bucharest, Romania); The 9th ADRE International Congress (2017, Iași, Romania; 2018, Bucharest, Romania); Connect Dentistry Summit (2020, Bucharest, Romania); MD-RO Summit 2nd Edition (2021, Bucharest, Romania); International Exhibition INVENTICA XXVI edition (2022, Iasi, Romania); "Traian Vuia" Invention Salon (2022, Timișoara, Romania); "Excellent Idea" Invention Exhibition (2022, Chisinau, Republic of Moldova). The approval of the thesis theme took place during the meeting of the Scientific Council of USMF "Nicolae Testemițanu" minutes no. 4 of November 21, 2017. The approval of the Research Ethics Committee for conducting the study was obtained during the meeting of 06.19.2017. The results were approved at the meeting of the Department of Therapeutic Dentistry of USMF "Nicolae Testemițanu" on 21.08.2021 and at the Specialized Scientific Seminar (scientific specialty 323. Dentistry) on 27.10.2022. **Publications on the topic of the thesis.** The basic materials of the thesis were published in 50 scientific papers, including 27 presentations/posters at various national and international scientific events (conferences, congresses, symposia), 1 synthesis article, 3 articles in national peer-reviewed journals (1 – category B and 2 – category C), 2 articles in international peer-reviewed journals, 16 summary communications published in the materials of international congresses and conferences, 3 published theses at national scientific events, 1 publication without co-authors, 2 invention patents. **The volume and structure of the thesis.** The text of the thesis is presented on 120 pages, consisting of: list of abbreviations, introduction, 5 chapters, general conclusions, practical recommendations, bibliography with 288 references and 4 appendices. The illustrative material includes 23 tables, 15 figures and 7 formulas. **Key words:** temporomandibular disorders, masticatory muscle dysfunctions, clinical-physiological indices, diagnosis.

2. MATERIAL AND RESEARCH METHODS

2.1. General characteristics, study design, inclusion/exclusion criteria

The planning of the cross-sectional study was based on the clinical examination materials of the patients, who were consecutively referred to the "Fala Dental" clinic, and on the clinical-neurophysiological investigations carried out at the "Neuronova" university clinic (Chisinau, Republic of Moldova). The investigations and the process of multidimensional analysis of the data were guided by the Department of Therapeutic Dentistry of the "Nicolae Testemițanu" State University of Medicine and Pharmacy.

Inclusion criteria: The presence of the patient's consent for participation in the research, cooperative patients; Female patients, aged between 18-45 years; Clinical diagnosis of masticatory muscle dysfunction based on the DC/TMD protocol (clinical variants: myogenous – *myalgia*; myogenous-arthrogenous – *myalgia+arthralgia*) according to the patient selection criteria recommended in the literature; Right-handed patients, corresponding for the quantitative-sensory tests; Patients in the first phase of the menstrual cycle (from the 5th to the 10th day), based on the recommendations regarding comparative studies in functional pain disorders. *Exclusion criteria:* The presence of other forms of temporomandibular disorders, with decompensated TMJ function or degenerative processes (confirmed by CBCT – cone beam computer tomography); Patients with orofacial pain originating outside the structures of the masticatory muscles or the temporomandibular joint; Recent traumas, surgical interventions in the TMJ region and masticatory muscles in the anamnesis; The presence of abnormalities and inflammatory signs in the stomatognathic system; Systemic diseases involving masticatory muscles and TMJ (rheumatoid arthritis,

scleroderma, septic arthritis, etc.).

According to the proposed purpose and objectives, a study design was created (Fig. 2.1), composed of conducting a series of experimental and clinical studies.

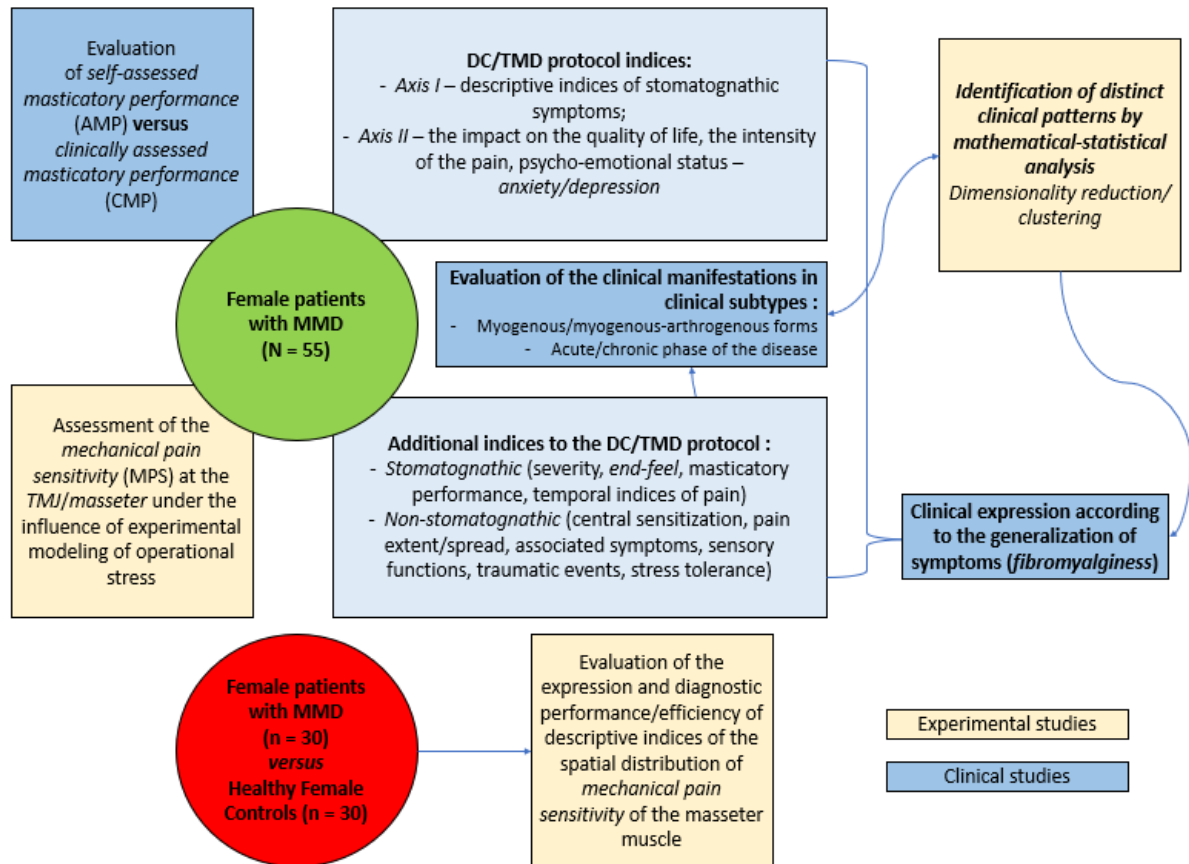


Fig. 2.1. Design of the study on patients with masticatory muscle dysfunctions

For the evaluation of clinical manifestations in different clinical subtypes, 55 patients with temporomandibular dysfunctions, diagnosed on the basis of DC/TMD, were included, of which 26 – myogenous forms and 29 – mixed myogenous-arthrogenous forms (myalgia+arthralgia). The age range was 18-43 years (Mean/SD – 28.1 ±5.02 years). The selection of female patients corresponds to data from epidemiological studies, which confirm that the age range most affected by TMD is represented by women aged 18-45 years, during the reproductive period [221]. To evaluate the expression and performance of descriptive indices of the spatial distribution of mechanical pain sensitivity, 60 female subjects, aged between 18-45 years (mean age 29.3±3.44 years) were enrolled in 2 groups: subjects with masticatory muscle dysfunctions (n = 30) and healthy subjects without MMD (n = 30).

2.2. Clinical examination (DC/TMD protocol/Additional indices to the protocol)

When examining stomatognathic clinical manifestations, the international standardized form (FDI) of the DC/TMD protocol for clinical examination (**Axis I**) [6] was used, with the following stages: *Collection of anamnestic data; Measurement of incisal relationships – overjet/overbite, midline deviation size; Evaluation of opening pattern; Assessment of range of motion (ROM); Evaluation of the presence of joint noises; Standardized palpation of masticatory muscles and the TMJ.*

There was applied the *Jaw Functional Limitation Scale (JFLS-8)* to assess the impact of pain and associated difficulties on the patient's quality of life (daily functionality) at the level of the patient's stomatognathic system. We used the *Di (Dysfunctional Index)*, proposed by Helkimo [7], to assess the severity of temporomandibular dysfunctions. The *Temporomandibular Index (TMI)*, proposed by Pehling et al., was determined. [8] for evaluating the degree of damage to the stomatognathic system. The index is

based on the assessment of the presence of clinical symptoms and the interpretation of the score on the functional subscales – Functional (TMI_F), muscular (TMI_M), articular (TMI_A), as well as the calculation of the total score. We used the TOI (*TMJ Opening Index*), proposed by Miller et al. [9] for the objective assessment of the clinical test to determine the *end feel*.

The *evaluation of the masticatory performance* was carried out by means of the Two-color chewing gum test, which assesses the patients' mixing ability. For the standardization of the test, specialized chewing gums – HueCheck Gum® (Orophys GmbH, Switzerland) were used. The subjective clinical interpretation of the test result was performed by visual inspection of the food bowl (chewed gum) and comparison with the masticatory performance classes (SA1-5) from the Subjective Assessment Scale (SAS), which gradually reflects the increase of masticatory performance from insufficient to very good. The objective interpretation of the result is achieved through the computerized analysis of the scanned image of the pressed gum by means of the ViewGUM specialized software (dHal Software, Spain), with the determination of the variance of hue index (VoH) [10]. Inadequate mixing of the food bowl is reflected in higher VoH scores compared to cases with complete mixing. We investigated the patient's subjective self-assessment of self-perceived masticatory performance on a VAS scale (0-10).

The following pain indices were assessed: current pain intensity ($GCPS_1$), maximum pain intensity in the last 30 days ($GCPS_2$) and average pain intensity in the last month ($GCPS_3$). We calculated the integrated pain intensity index – CPI (*Characteristic Pain Intensity*). The assessment of pain frequency/duration was made based on the temporal subscales of the SSI questionnaire [11], the assessment being made separately for arthralgia and myalgia.

For the clinical assessment of central sensitization, there was used the Central Sensitization Inventory CSI-9 (9-item shortened form). The degree of pain expansion was determined based on the Widespread Pain Index (WPI) [12] which includes 19 items (body areas), represented on 2 body maps (front view, back view). To assess the impact of extended pain, the Symptomatic Severity Index was used, represented by the total score on the SSS (Symptom Severity Scale) scale for symptoms associated with extensive pain.

In accordance with the study objectives, the self-perception of sensory stimuli (*Allergy, Heat, Cold, Light, Pain, Smell, Hearing, Taste, Touch*) was investigated on the SHS scale, as well as the total level of self-perceived sensory sensitivity, depending on clinical subtypes of masticatory muscle dysfunction [13].

We applied the *two-point discrimination* (TPD) test to evaluate mechano-perception, with the determination of the static index of mean tactile sensitivity (MTS) based on the method proposed by Won et al. [14]. We used the algometry method to assess mechanical pain sensitivity at the level of stomatognathic (TMJ, masseter muscle) and extra-stomatognathic structures (reference site – hypothenar region). Pressure pain threshold (PPT), pain tolerance threshold (PTT) and pressure pain endurance (PPE) data were collected per each site. Quantitative-sensory dynamic indices of pain intensity perception during vibrotactile stimulation were assessed in 3 anatomical sites: forearm (reference area), masseter muscle and TMJ (stomatognathic sites), based on the method proposed by Nixdorf et al. [15]

To evaluate the spatial distribution of *mechanical pain sensitivity* (MPS) of the masseter muscle, the following experimental analysis algorithm was developed and applied: algometry of the masseter muscle for a 3×3 pain map configuration composed of 9 PPT thresholds (pain pressure threshold mapping); followed by mathematical processing of the collected data, with the calculation of: centrality parameters (COG-DC, COG-A), affected muscle surface (%), PPT descriptors (minimum value, maximum value; mean value and standard deviation); diversity indices (Shannon entropy, standard deviation). An integral parameter was developed to describe the degree of homogeneity/non-uniformity of the spatial distribution of MPS (Patent MD 1608 Y, BOPI no. 3/2022) [16], with the simultaneous characterization of the degree of differentiation and diversity of the PPT thresholds – *relative heterogeneity* (H_{rel}), according to the formula: $H_{rel} = \frac{\sigma S}{\bar{A}}$.

The level of anxiety was assessed by the GAD-7 (Generalized Anxiety Disorder-7) questionnaire, developed by Spitzer et al. [17]. The level of depression was assessed using the PHQ-9 questionnaire (Patient Health Questionnaire – 9), developed by Kroenke et al. [18]. The level of perceived psychological distress was determined based on the Kessler Psychological Distress questionnaire (K10), which contains 10 items about emotional states, rated on a 5-level Likert scale. The anamnestic screening of past traumatic events was carried out by means of the THS (Trauma History Screen) questionnaire, with the determination of the total number of traumatic events (NTE), the total number of acute stress disorders (NASD) and the age of the first traumatic event (AFTE).

The experimental modeling of operational stress was carried out by means of the specialized software SkyTest® (Germany), within the Stress Tolerance Test module, with the determination of the stress-tolerance index (STO). The level of operational stress (STR) caused was self-assessed by the patient on a VAS scale (0-10), according to the method proposed by Lesage et al. [19].

2.3. Mathematical-statistical processing

Primary collected data were stored in databases in Excel 2019 software (Microsoft, USA), with further processing in the statistical analysis program SPSS v.26 (IBM, USA). Initially, the normality of data distribution was checked by means of the Shapiro-Wilk test. For scalar variables, the arithmetic mean and standard error (SE) were determined as indicators of central tendency by group. Welch's t-test was used to examine group differences in the means of scalar variables. Indices that demonstrated significant trends of change between subgroups were later statistically analyzed regarding the odds ratio (OR), with the 95% confidence interval (95% CI), with only the significant cases being reported. The Wilcoxon non-parametric paired test was used to evaluate the change over time of certain variables (pre- and post-operational stress modeling). By applying the simple linear regression model, the relationship between independent variables and dependent variables was determined, with the identification of the B (beta) coefficient value. For the veracity of the given method selection, the assumptions of normality and homoscedasticity of the data were checked. To examine differences between groups for nominal variables, contingency tables (Pearson's Chi-square test, Fisher's exact test and Likelihood Ratio Test) and the Cochran-Armitage trend test were used. There were used the Pearson (parametric), Spearman and Kendall (non-parametric) correlation coefficients and the partial correlations, depending on the type of data and based on respecting the linearity of the relationships between each pair of variables. To evaluate the degree of correspondence between the subjective indices of masticatory performance (AMP/CMP), the rescaling of the data was carried out, using the method recommended by Anderson et al. [20] regarding the evaluation in different response groups based on Δ ($\Delta=0$, $\Delta<0$, $\Delta>0$). Dimensionality reduction of the data was achieved through the feature selection procedure, according to the methodology proposed by Burns et al. [21] in several iterations by filtering the initial variables (pre-standardized), followed by clustering, by means of the modified k-means++ algorithm in the specialized statistical software PQStat (PQStat Software, Poland). The evaluation of the performance of the descriptive indices of mechanical pain sensitivity (MPS) in differentiating MMD cases from non-cases was carried out by means of the ROC curves (*receiver operating characteristic curve*), their comparative analysis, the calculation of the AUC (*area under the curve*) indices, the Youden index (J) and sensitivity/specificity per tested parameter. In all types of statistical analysis, data were considered significant for $p < 0.05$. The results of the statistical processing were presented in tables and graphs, highlighting the higher values per subgroups and the statistically significant probabilities.

3. THE PARTICULARITIES OF THE CLINICAL MANIFESTATIONS OF THE MASTICATORY MUSCLE DYSFUNCTION

We used the following criteria when dividing patient subgroups:

- 1) *Location or clinical variant/form* – based on recommendations for separate investigation of diagnostic subgroups of masticatory muscle dysfunctions (*myogenous/myogenous-arthrogeous*), depending on the involvement in the pathogenetic processes of different structures of the stomatognathic system [22]. Thus, from the total group (TG) of MMD patients (N = 55), there were divided 2 groups:

myogenous (M, n = 26) and myogenous-arthrogenous/mixed variant (MA, n = 29), in which there is a co-presence of myalgia and arthralgia.

2) *Phase of the disease (acute/chronic)* – it is recommended to use the duration of 6 months from the onset of the dysfunction (reported in the anamnesis) as a landmark for the transition to the chronic phase [23]. From the total group of patients with masticatory muscle dysfunctions, the AD (acute disorders, n = 31) and CD (chronic disorders, n = 24) groups were divided.

3.1. The structure of the disease symptomatology (DC/TMD protocol) depending on the clinical variant/phase of the disease

In patients with masticatory muscle dysfunction (N = 55), for the muscle sites evaluated in the DC/TMD protocol, positive symptoms in the anamnesis are more characteristic ($\geq 50\%$) for the temporalis and masseter muscles compared to other masticatory muscles (lateral pterygoid, medial pterygoid, digastric), and for non-muscular sites; and for non-muscular sites, a higher frequency was observed for TMJ compared to non-masticatory sites (other orofacial regions). Headache complaints had a high frequency, more frequently in the projection of the temporal region than in other cranial regions. The observed trends were evaluated based on the strength of the association between the analyzed criteria (clinical variant/disease phase) and the presence of the symptom. It was observed that in the myogenous-arthrogenous variant compared to the myogenous one, there is an increased chance of the presence of anamnestic pain at the TMJ level (OR = 3.34, p = 0.037, 95% CI – 1.074, 10.385); while in the chronic phase compared to the acute one, higher chances are observed for the presence of anamnestic pain at the level of the temporal muscle (OR = 3.36, p = 0.035, 95% CI – 1.083, 10.44) and non-masticatory structures (OR = 4.05, p = 0.040, 95% CI – 1.064, 15.40), as well as for headaches with projections in other cranial areas (OR = 8.33, p < 0.001, 95% CI – 2.434, 28.525). In the myogenous-arthrogenous variant compared to the myogenous one, there is an increased chance of evoking pain when performing: the *unassisted opening movement* (passive opening, PO) for other masticatory muscles (OR = 11.25, p = 0.027, 95% CI – 1.313, 96.393); *assisted opening movement* (active opening, AO) for temporal muscle (OR = 5.40, p = 0.044, 95% CI – 1.044, 27.92), TMJ (OR = 7.98, p = 0.001, 95% CI – 2.309, 27.575); other masticatory muscles (OR = 11.25, p = 0.027, 95% CI – 1.313, 96.393) of the *right laterotrusion movement* (RL) for TMJ (OR = 4.46, p = 0.023, 95% CI – 1.227, 16.275) of the *left laterotrusion movement* (LL) for TMJ (OR = 24.56, p = 0.03, 95% CI – 1.349, 447.140). In the chronic variant compared to the acute one, there is an increased chance of evoking pain when performing: the *unassisted opening movement* (PO) for the masseter muscle (OR = 3.03, p = 0.049, 95% CI – 1.002, 9.162), TMJ (OR = 3.64, p = 0.02, 95% CI – 1.137, 11.662) and non-masticatory structures (OR = 5.97, p = 0.037, 95% CI – 1.110, 32.089); *assisted opening movement* (AO) for TMJ (OR = 5.75, p = 0.003, 95% CI – 1.785, 18.515); *left laterotrusion movement* (LL) for other masticatory muscles (OR = 53.67, p = 0.007, 95% CI – 2.945, 977.663). It should be noted that, on palpation, statistically significant according to the *clinical variant* criterion, are the trends of increased frequencies for TMJ sites (lateral pole, proximal region to the lateral pole), while according to the *disease phase* criterion, a statistically significant increase both in TMJ sites (the region close to the lateral pole of the TMJ) and at muscle sites – the posterior portion of the temporal muscle (OR = 8.70, p = 0.01, 95% CI – 1.663, 45.48) and the insertion of masseter muscle. It should be noted that during static palpation of the TMJ, a higher frequency of painful signs is observed when palpating the regions proximal to the TMJ lateral pole (over 80%), than when palpating the lateral pole itself (23.1-44.8%). It was also observed that all patients in the MA and CD groups had a painful response when palpating the region proximal to the lateral pole of the TMJ. Depending on the clinical variant, in the myogenous-arthrogenous group, statistically significantly higher mean values are observed for the overbite, pain indices (current pain, maximum pain, integrative pain intensity index) and for the oral health quality of life impact index (functional limitation of the stomatognathic system – JFLS-8); and for the amplitude of the *left laterotrusion movement* (LL), statistically significantly lower values are recorded compared to the myogenous group, the other indices not showing statistically significant differences between the groups.

Table 3.1. Mean values of quantitative clinical indices (DC/TMD protocol) in masticatory muscle dysfunction versus clinical variant and disease phase

Index groups	Indices	TG (N = 55)	M (n = 26)	MA (n = 29)	<i>p</i> 2 vs 1	AD (n = 31)	CD (n = 24)	<i>p</i> 4 vs 3
			1	2		3	4	
Occlusal parameters	<i>Overjet</i>	2.72 (0.17)	2.85 (0.21)	2.60 (0.28)	0.497↔	2.51 (0.20)	2.97 (0.31)	0.221↔
	<i>Overbite</i>	4.89 (0.32)	4.17 (0.39)	5.53 (0.47)	0.016 ↑	4.75 (0.51)	5.06 (0.34)	0.625↔
	MDV	0.95 (0.09)	1.10 (0.17)	0.82 (0.09)	0.180↔	0.95 (0.13)	0.95 (0.14)	0.973↔
Range of motion (ROM)	PFO	33.4 (1.31)	34.85 (2.25)	32.17 (1.46)	0.325↔	35.77 (1.85)	30.41 (1.68)	0.037 ↓
	PO	46.1 (0.88)	46.04 (1.50)	46.06 (1.01)	0.987↔	47.67 (1.03)	43.95 (1.43)	0.041 ↓
	AO	50.3 (0.84)	49.46 (1.46)	50.96 (0.93)	0.392↔	51.95 (0.93)	48.06 (1.42)	0.028 ↓
	RL	10.9 (0.41)	10.92 (0.65)	10.81 (0.54)	0.894↔	10.72 (0.54)	11.04 (0.65)	0.712↔
	LL	9.91 (0.29)	10.62 (0.38)	9.27 (0.40)	0.010 ↓	10.43 (0.42)	9.22 (0.34)	0.033 ↓
	PR	7.62 (0.29)	7.98 (0.41)	7.29 (0.42)	0.253↔	7.69 (0.39)	7.52 (0.46)	0.779↔
QoL	JFLS	1.60 (0.23)	1.13 (0.20)	2.02 (0.38)	0.025 ↑	1.23 (0.24)	2.08 (0.41)	0.042 ↑
Pain indices	<i>GCPS₁</i>	3.33 (0.37)	2.65 (0.53)	3.93 (0.50)	0.043 ↑	2.22 (0.45)	4.75 (0.49)	< 0.001 ↑
	<i>GCPS₂</i>	5.91 (0.33)	5.15 (0.45)	6.58 (0.45)	0.015 ↑	5.67 (0.40)	6.20 (0.55)	0.444↔
	<i>GCPS₃</i>	4.09 (0.24)	3.69 (0.31)	4.44 (0.37)	0.127↔	4.25 (0.32)	3.87 (0.39)	0.456↔
	<i>CPI</i>	44.4 (2.73)	38.33 (3.84)	49.88 (3.62)	0.017 ↑	40.53 (3.43)	49.44 (4.26)	0.111↔

Note: Values are presented as mean (standard error); ↓ – the mean values in group 2(4) are lower than those in group 1(3); ↑ – the average values in group 2(4) are higher than those in group 1(3); ↔ – non-significant differences between means. Abbreviations: TG – the total group; AD – acute disorders; CD – chronic disorders; MDV – midline deviation; PFO – pain-free opening; PO – passive opening; AO – active opening; RL – right laterotrusion; LL – left laterotrusion; PR – protrusion; JFLS – jaw functional limitation scale; GCPS₁ – current pain intensity; GCPS₂ – mean pain intensity; GCPS₃ – maximum pain intensity; CPI – characteristic pain intensity. Statistical analysis used: Welch’s t-test (*p_w*).

Depending on the disease phase criterion, it was observed that in the group with chronic disorders, there were statistically significantly higher average values for the JFLS-8 index, current pain intensity (GCPS₁) and statistically significantly lower values compared to the group with acute disorders for the amplitude of all *opening movements* (pain free opening, passive opening, active opening) and *left laterotrusion* (LL), the other indices not revealing differences between groups. Among the pain intensity indices, only the current pain intensity (GCPS₁) showed a significant increase in values in patients with the chronic phase of the disease (*p* < 0.001).

3.2. The structure of the disease symptomatology (additional indices to DC/TMD) versus the clinical variant/phase of the disease

For indices that are not part of the DC/TMD protocol, differences were observed depending on the *clinical variant* (M/MA) and the *disease phase* (AD/CD), attesting to a number of peculiarities. Statistically significantly higher values were observed for the severity indices (Helkimo dysfunctional index, temporomandibular index), as well as for the its *Articular subscale* (TMI_A); indices of duration and frequency of muscle pain (DM_{SSI}, FM_{SSI}), as well as for the descriptor index of the *end-feel* sensation (TOI), the other indices did not reveal differences between the groups. The indices from the DC/TMD protocol regarding the *amplitude of passive opening* (PO) and *active opening* (AO) did not show statistically

significant differences according to the clinical variant (M/MA), but the TOI index demonstrated statistically significantly higher values in the myogenous-arthrogenous group versus the myogenous one ($p < 0.05$). The almost similar mean values of the Mandibular Mobility Index (MMI) in patients with myogenous and myogenous-arthrogenous forms confirm previous observations regarding similar values of the amplitude of the range of motion (assessed in the DC/TMD protocol), regardless of the clinical variant, except for the movement of left laterotrusion, which presented lower values in the myogenous-arthrogenous variant compared to the myogenous one.

Tab. 3.2. Mean values of quantitative clinical indices (additional to DC/TMD protocol) in masticatory muscle dysfunction versus clinical variant and disease phase

Index groups	Indices	TG (N = 55)	M (n = 26)	MA (n = 29)	p_w 2 vs 1	AD (n = 31)	CD (n = 24)	p_w 4 vs 3
			1	2		3	4	
Mobility	MMI	2.64 (0.32)	2.42 (0.47)	2.82 (0.45)	0.540↔	2.06 (0.40)	3.37 (0.49)	0.024↑
Severity	Di	16.2 (0.61)	13.84 (1.04)	18.24 (0.44)	< .001↑	14.35 (0.89)	18.50 (0.54)	< 0.001↑
	TMI _F	0.39 (0.02)	0.36 (0.03)	0.42 (0.02)	0.240↔	0.32 (0.02)	0.47 (0.03)	< 0.001↑
	TMI _M	0.67 (0.02)	0.68 (0.04)	0.67 (0.03)	0.804↔	0.65 (0.03)	0.70 (0.03)	0.309↔
	TMI _A	0.40 (0.03)	0.20 (0.02)	0.58 (0.04)	< .001↑	0.34 (0.04)	0.48 (0.05)	0.027↑
	TMI	0.49 (0.02)	0.41 (0.03)	0.55 (0.02)	< .001↑	0.44 (0.02)	0.55 (0.02)	0.003↑
End-feel	TOI	4.46 (0.41)	3.70 (0.46)	5.14 (0.65)	0.040↑	4.37 (0.51)	4.56 (0.70)	0.835↔
Masticatory performance	MVAS	6.67 (0.22)	6.84 (0.35)	6.51 (0.27)	0.469↔	6.90 (0.32)	6.37 (0.28)	0.227↔
	VOH	0.21 (0.01)	0.18 (0.02)	0.24 (0.03)	0.125↔	0.27 (0.02)	0.14 (0.02)	0.001↓
Temporal pain indices	DM _{SSI}	2.24 (0.13)	1.92 (0.14)	2.51 (0.21)	0.013↑	2.12 (0.20)	2.37 (0.17)	0.364↔
	DA _{SSI}	1.62 (0.21)	1.26 (0.31)	1.93 (0.27)	0.121↔	1.45 (0.30)	1.83 (0.29)	0.367↔
	FM _{SSI}	2.25 (0.14)	2.00 (0.15)	2.48 (0.21)	0.040↑	2.35 (0.20)	2.12 (0.18)	0.408↔
	FA _{SSI}	1.22 (0.19)	1.07 (0.30)	1.34 (0.24)	0.498↔	1.35 (0.29)	1.04 (0.23)	0.408↔

Note: Values are presented as mean (standard error); ↓ – the mean values in group 2(4) are lower than those in group 1(3); ↑ – the average values in group 2(4) are higher than those in group 1(3); ↔ – non-significant differences between means. Abbreviations: TG – the total group; AD – acute disorders; CD – chronic disorders; MMI – mandibular mobility index; Di – Helkimo Dysfunctional Index; TMI_F – Functional TMI Subscale; TMI_M – Muscular TMI Subscale; TMI_A – Articular TMI Subscale; TMI – Temporomandibular Index; TOI – Temporomandibular Opening Index; MVAS – self-perceived masticatory performance (VAS); VOH – variance of hue; DM_{SSI} – Duration of myalgia (SSI Subscale); DA_{SSI} – Duration of arthralgia (SSI Subscale); FM_{SSI} – Frequency of myalgia (SSI Subscale); FA_{SSI} – Frequency of arthralgia (SSI Subscale). Statistical analysis used: Welch's t-test (p_w).

The functional capacities based on the TMI_F scale (an integrative index summarizing the clinical indices regarding the range of motion, the presence of pain on motion, incisal relations, the pattern of opening and the type of deviation) do not reveal statistically significant differences between the myogenous and myogenous-arthrogenous groups, having values approximately equal, but the functional limitation scale (JFLS-8) from the DC/TMD protocol, reveals that in people with myogenous-arthrogenous forms, the limitations felt by the patient are statistically significantly higher ($p < 0.05$).

The TMI severity index presented statistically significant differences between groups ($p < 0.001$), having higher mean values (increased severity) in the myogenous-arthrogenous variant, but when analyzing its subscales, there were observed similar mean values and the lack of statistically significant differences for the Muscular (TMI_M) and the Functional (TMI_F) subscales, the only subscale with statistically significant changes was the Articular one (TMI_A) ($p < 0.001$), which would indicate that on average, patients with the myogenous and myogenous-arthrogenous variants show similar levels of functional and muscular impairment, but the decisive factor in amplifying the severity is the degree of TMJ impairment. These differences in total severity are also confirmed by the classic Helkimo severity index (Di), which presents statistically significantly higher values in the myogenous-arthrogenous variant ($p < 0.001$). Also, the indices of frequency and duration of pain (myalgia/arthritis) reveal that in the myogenous-arthrogenous variant, both the duration and frequency of muscle pain increase statistically significantly ($p < 0.05$), while joint pains do not show statistically significant differences, the duration and the frequency being almost similar in both clinical variants (myogenous, myogenous-arthrogenous). There are also no differences in the number of affected muscle sites (TMI) between the groups, depending on the clinical variant. At the level of masticatory performance, no statistically significant differences were identified, depending on the clinical variant (M/MA), both at the level of objective index (VoH) and subjective indices (self-assessment of masticatory performance – MVAS).

As a function of the disease phase, stomatognathic indices that are not part of the DC/TMD protocol, which show statistically significantly higher values, are indices of the severity of the disorders (mandibular mobility index, Helkimo dysfunctional index, temporomandibular index – TMI), as well as for the Articular subscale (TMI_A); indices with statistically significantly lower values compared to the group of acute disorders (AD) are the objective index of masticatory performance (VoH), the other indices not revealing differences between the groups. Although in the chronic group, statistically significantly lower mean values for opening movement amplitude parameters for indices from the DC/TMD protocol (pain-free opening, passive opening, active opening) are attested ($p < 0.05$), this is not reflected in the index TOI (composite index based on the differences between active and passive opening), where there weren't observed any statistically significant differences between groups. The functional indices of the amplitude of the functional movements in the DC/TMD protocol (pain-free opening, passive opening, active opening, left laterotrusion) reveal a statistically significant reduction in the mean values ($p < 0.05$), this being also reflected in the increase of the severity level in the mandibular mobility index (MMI) ($p < 0.05$) and of the Functional subscale of the TMI (TMI_F) ($p < 0.001$). This is also observed in statistically significantly higher means of the JFLS index ($p < 0.05$) regarding the limitation of the ability to perform the functions of the stomatognathic system (mastication, speech, swallowing, etc.).

With the transition to the chronic phase, statistically significantly higher mean values are observed for severity indices (TMI, Di) ($p < 0.001$), but clinical signs are statistically significantly different mostly only for range of motion (ROM) indices, but not for pain indices (except current pain intensity – GCPS₁). Depending on the phase of the disease, no statistically significant differences were observed both according to pain intensity (except for current pain – GCPS₁, which increases significantly in patients with the chronic form – $p < 0.001$), duration and frequency of myalgia and arthralgia depending on disease phase. There are also no differences in the number of affected muscle sites (TMI_M) between the groups according to the phase of the disease.

The masticatory performance self-assessed by the patient does not reveal statistically significant

differences according to the mean values between the acute and chronic groups, but the computerized objective parameter (VoH) shows statistically significantly lower values in the chronic group ($p < 0.001$), which reveals the presence of differences in mixing ability using 2 standardized gums, the higher values observed in the acute group signifying lower masticatory performance.

In the context of revealing the influence of masticatory muscle dysfunctions on mandibular mobility (ROM), as well as on the daily functionality of patients (JFLS-8), it is promising to investigate the function of mastication, by revealing masticatory performance, based on the use of the test of mixing 2 chewing gums with different colors, proposed by the team of Prof. Schimmel M. [10]. Previously, trends of statistically significant changes in the computerized quantitative index VoH (*variance of hue*) were observed depending on the phase of the disease, as well as the presence of some discordances regarding the levels of subjective assessment by patients of the masticatory performance and the computerized quantitative VoH index.

For the convenience of application in wide dental practice, the authors proposed a clinical visual scale, for classifying the level of masticatory function impairment, based on the properties of the food bowl (SAS Scale). We performed the analysis of the frequencies of the different classes of masticatory performance, according to SAS, in the total group, as well as according to the clinical variant and the phase of the disease criteria in patients with masticatory muscle dysfunctions. The frequency of severe disorders of mastication (SA2) is reduced in patients with MMD (7.3%); depending on the clinical variant, roughly similar proportions were observed (M – 7.7%; MA – 6.9%), while in the chronic disorders group there were no subjects with this class compared to people with the acute phase (12.9%). In patients with MMD, no subjects with extreme values (SA1 – very severely affected masticatory performance or SA5 – excellent masticatory performance) were identified, the medium (SA3) and good (SA4) variants of masticatory performance being approximately equally attested in the sample, without statistically significant differences between the groups depending on the clinical variant and the phase of the disease criteria (Likelihood Ratio test, $p = 0.906$, respectively $p = 0.0816$).

According to Schimmel [10], higher VoH values indicate a lower masticatory performance, a fact confirmed by the negative, statistically significant correlation between the VoH value and masticatory performance assessed on the SAS scale ($\tau = -0.362$, $p < 0.001$).

In the context of revealing a discordance between the values of the objective VoH index and the subjective index of masticatory performance self-reported by the patient (MVAS), we further investigated whether there is a degree of correspondence. Thus, the data on self-reported masticatory performance (AMP) (VAS 0-10) were transformed into a 5-level Likert system, similar to the scale used for SAS, followed by the verification of the degree of correspondence, by calculating Δ (the difference between SAS and re-scaled VAS), for the differentiation of 3 categories: V1 – correspondence of self-reported masticatory performance (AMP) with that clinically assessed on the SAS scale (CMP) ($\Delta = 0$), V2 – AMP > CMP ($\Delta < 0$) and V3 – AMP < CMP ($\Delta > 0$). In the total group (TG), a predominance of V1 was identified (45.5%, $n = 25$); followed by V2 (40%, $n = 22$) and V3 (14.5%, $n = 8$), the differences in proportions being statistically significant ($p_w = 0.024$). Depending on the clinical variant, it was observed that in the myogenous group, the distribution of variants V1, V2, V3 was 42.30% ($n=11$), 46.15% ($n = 12$), respectively 11.53% ($n = 3$) ($p_w = 0.015$); in the myogenous-arthrogenous variant – V1 – 48.27%, $n = 14$; V2 – 34.48%, $n = 10$, V3 – 17.24%, $n = 5$, without statistically significant differences between proportions ($p_w = 0.253$). Depending on the phase of the disease, it was observed that in the group of acute disorders, the distribution of variants V1, V2, V3 was 45.16% ($n=14$), 45.16% ($n = 14$), respectively 9.67% ($n = 3$) ($p_w = 0.011$); in the chronic variant – V1 – 45.83%, $n = 11$; V2 - 33.33%, $n = 8$, V3 – 20.83%, $n = 5$, without statistically significant differences between proportions ($p_w = 0.416$). In subjects with myogenous and acute variants of masticatory muscle dysfunction, there is a tendency of significant increases in the frequency of overestimation of masticatory performance by patients (AMP), compared to the clinically determined level (CMP).

Thus, in order to appreciate the observed differences in the expression of quantitative clinical indices of masticatory muscle dysfunctions (both indices from the DC/TMD protocol and those addition to it), we have summarized the observed results, regarding the trends of index changes in the differentiation of clinical cases based on the criteria *clinical form, phase of the disease*, the statistically significant change of which is differently associated with the *clinical variant* and *phase of the disease* criteria. A variety of the composition of the groups of indices was observed, according to their behavior according to the analyzed criteria (*clinical form, phase of the disease*), there being no clear differentiation according to the nature of the indices and the phenomena being measured, which denotes a significant heterogeneity of the diagnostic results for the analyzed criteria (*disease phase, clinical variant*).

3.3. Manifestation patterns of masticatory muscle dysfunction (cluster analysis)

We used the methodology of filtering and selection of clinical characteristics (feature selection), proposed by Burns et al. [21] to determine distinct patterns of manifestation of masticatory muscle dysfunction by means of a modified clustering algorithm (k-means++). Based on this procedure, the clinical indices collected from the patients were analyzed (63 continuous variables), which after 6 iterations of the filtering procedure led to the determination of 8 variables (4 – from the DC/TMD protocol, 4 – additional to the DC/TMD protocol), which according to the p-value, following ANOVA and the test of homogeneity of variances F (Welch's correction) demonstrated a significant ability to separate clinical cases into cluster groups (Table 3.3).

The adequacy of the number of clusters (k) was verified based on re-clustering with a different number of clusters (k value from 2 to 5), with the verification of silhouette scores regarding the quality of the obtained clusters. For the value k = 2, a higher average silhouette score was established (0.339). Subsequently, the visual analysis of the degree of separation of the clinical cases at the inter-cluster level was carried out, establishing an adequate dispersion of the cases per cluster, without the predominance of subjects with extreme values (outliers) or non-separated.

Tab. 3.3. The average values of the features selected for clustering

Features		Cluster 1 (n = 26)	Cluster 2 (n = 29)	<i>p</i> (ANOVA)	<i>p</i> (Welch F)
DC/TMD indices	<i>Pain-free opening size</i>	29.92±9.72	36.59±8.8	0.010062	0.010572
	Characteristic pain intensity (CPI)	52.56±18.39	37.13±19.27	0.003762	0.003686
	Total score, anxiety (GAD-7)	11.5±4.32	4.14±2.56	<0.000001	<0.000001
	Total score, depression (PHQ-9)	10.12±4.74	4.24±2.64	<0.000001	0.000002
Indices additional to DC/TMD	Total Score, Central Sensitization (CSI-9)	21.73±4.08	12.83±4.95	<0.000001	<0.000001
	Total score, pain extent (WPI)	9.04±3.29	3.24±1.79	<0.000001	<0.000001
	Total score, symptom severity (SSS)	5.62±2.33	1.69±1.87	<0.000001	<0.000001
	Total score, distress (K10)	29.31±7.12	16.59±4.16	<0.000001	<0.000001

Note: Data per cluster are presented as means/standard deviations.

Based on the processing performed, 2 clusters were identified for patients with masticatory muscle dysfunction (N = 55), with a distinct pattern of clinical expression. The clinical interpretation of the mean values of the clinical clustering characteristics was performed according to the norms of the specialized literature [6].

The obtained clusters allow the optimization of the diagnostic process and monitoring of the patient during the treatment process. To illustrate the clinical patterns determined by clustering, we performed the analysis of 2 clinical cases (patients AP and XB) with masticatory muscle dysfunctions, regarding the effectiveness of reversible occlusal therapy based on the change in dysfunction severity indices (Di) [7] and clinical characteristics used for clustering.

Results of the clinical examination. Following the clinical examination, both patients had a similar diagnosis – Myogenous temporomandibular dysfunction – myalgia (diagnosis based on the DC/TMD protocol), chronic phase (> 6 months), severity of dysfunction (Di) – 7 (dysfunctional group 2 – moderate dysfunction). Based on the clinical characteristics used for clustering, the patients were part of 2 different clusters – patient AP – Cluster 2, predominance of regional disorders (RD), and patient XB – Cluster 1, predominance of generalized disorders (RGD) (Table 3.4).

	<i>Feature</i>	Cluster 1 (regional-generalized disorders – RGD)	Cluster 2 (regional disorders – RD)
DC/TMD indices	<i>Limitation of PFO</i>	increased (PFO<30 mm),	mild (PFO <40mm)
	<i>Pain intensity (CPI)</i>	high (CPI>50%)	low (CPI<50%)
	<i>Anxiety level (GAD-7)</i>	moderate (GAD7>10)	mild (GAD7<5),
	<i>Depression level (PHQ-9)</i>	moderate (PHQ9>10)	minimal (PHQ-9<5).
Indices additional to DC/TMD	<i>Central sensitization level (CSI-9)</i>	severe (CSI-9>20)	mild (CSI-9>10),
	<i>Distress level (K10)</i>	severe (K10>22)	moderate (K10<22)
	<i>Pain extent (WPI)</i>	increased (WPI>7)	reduced (WPI<7)
	<i>Symptom severity (SSS)</i>	increased (SSS>5)	reduced (SSS<5)

Table 3.4. Initial clinical examination data of patients AP and XB

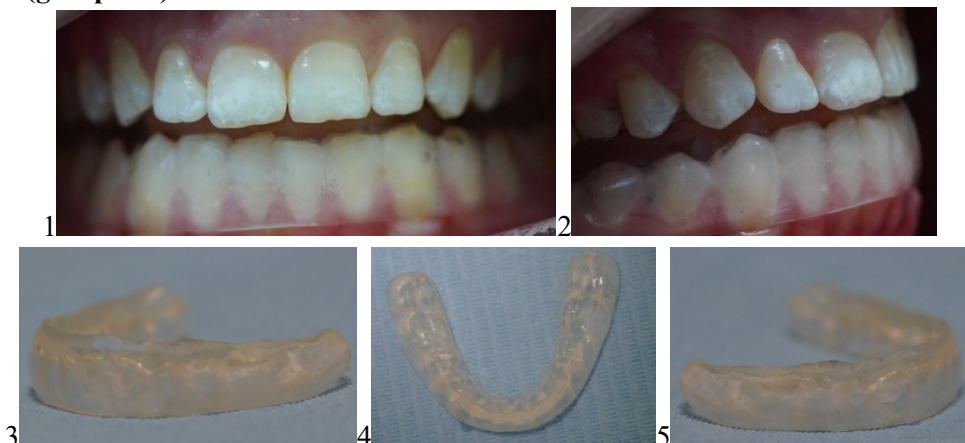
<i>Features</i>		Patient AP (Cluster 2 – RD)	Patient XB (Cluster 1 – RGD)
DC/TMD indices	PFO, mm	36 (slight limitations)	28 (marked limitations)
	CPI, %	43,33% (low intensity)	40% (low intensity)
	GAD-7, un.	3 (minimum level)	15 (severe level)
	PHQ-9, un.	3 (minimum level)	10 (moderate level)
Indices additional to DC/TMD	CSI-9, un.	6 (subclinical level)	21 (moderate-severe level)
	K10, un.	11 (minimum level)	23 (severe level)
	WPI, un.	3 (reduced level)	8 (marked level)
	SSS, un.	1 (reduced level)	6 (severe level)

Applied treatment. Based on the clinical diagnosis, the same type of reversible occlusal therapy was applied to the patients – the occlusal splint for muscle rehabilitation and stabilization [25], with indications for non-stop use (except for meals) (Figure 3.1). The evaluation of the effectiveness of the treatment was done after one month of treatment (intermediate evaluation stage), by re-evaluating the dysfunctional status (severity – *Di*) as well as the values of the clinical characteristics (*features*) used in clustering. The patients complied with the regimen of wearing the splints, and came to the splint adjustment visits. In patient AP (Cluster 2 – predominance of regional disorders) a reduction in the severity of dysfunction was observed (decrease in the Helkimo *Di* index 7 → 3, which corresponds to dysfunctional group 1 – minor dysfunction), and in patient XB (Cluster 1 – predominance of regional-generalized disorders) there was observed a worsening of the condition (increased *Di*, 7 → 11, transition from dysfunctional group 2 – dysfunction with moderate severity – to group 3 – severe dysfunction).

The response to treatment is different, although the initial clinical dental diagnosis is similar (including skeletal class). In the AP patient, an improvement in functional indices is observed, as well as a stability or slight improvement in additional clinical indices, a fact also confirmed by the patient's subjective evaluation of his own condition. In patient XB, there was observed a general trend of worsening of both the functional indices and the persistence/worsening of the intensity of the general symptoms, revealed by additional examinations. The patients were questioned regarding the subjective evaluation of the effect of the reversible occlusal treatment on the state of the stomatognathic system. The AP patient (Cluster 2,

predominance of regional disorders) reported that already after a week of wearing the splint, the frequency of pain symptoms decreased, functional movements (opening, laterotrusion, protrusion) became more comfortable, she already manages to open larger the oral cavity, she does not tire as much during chewing, no longer feels tension or spontaneous pain in the masticatory muscles, the frequency of headaches has significantly reduced. Patient XB (Cluster 1, predominance of regional-generalized disorders) reported increasing discomfort while wearing the splint, especially irritation and a tendency to directional focus and forceful clenching of the brace, especially under stress. Although initially there was a period of improvement, this was transient, and they generally rate the current condition as worsening. The feeling of tension in the masticatory and cervical muscles persists. The patient also associates these sensations with periods of increased stress and agitation. She also accuses the presence of new pains in other regions of the body and the persistence of a general psychological discomfort. From the subjective evaluation of patient XB, it is confirmed that after 1 month of treatment, a general state of discomfort, irritation and worsening of dysfunctional symptoms persists, especially during periods of increased stress, the patient mentioning that the general state of daily "stress" persists, something also confirmed by the results of psychoemotional evaluation questionnaires. Based on the recommendations from the specialized literature [2], patient XB was recommended a specialized examination by a neurologist and a kinesiologist, following which, in parallel with the functional therapy, an interdisciplinary treatment regime would be carried out: psychological counseling; neurological treatment – antidepressants, anxiolytics, muscle relaxants, vegetotropics; kinetherapeutic treatment – post-isometric relaxation, taping.

Patient AB (group DR)



Patient XB (group DRG)

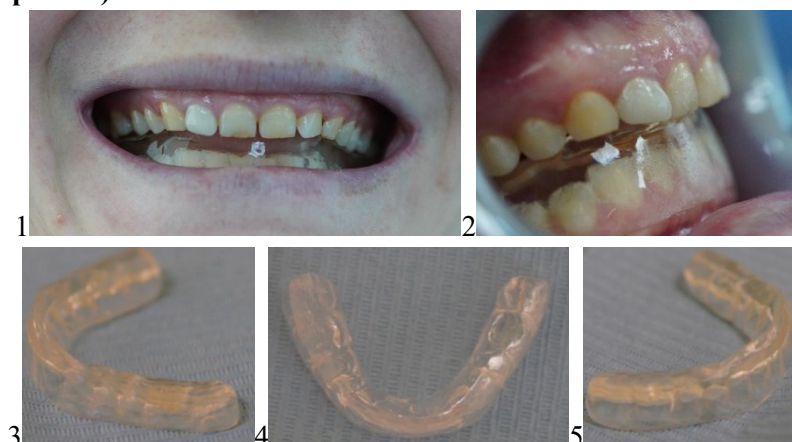


Figure 3.1. Reversible occlusal treatment (muscle reconditioning and stabilization splint), in patients with masticatory muscle dysfunction.

The appearance of the splint – *Tooth gearing*: 1 – frontal view, 2 – right lateral view; *Design*: 3-5 –left lateral/superior/right lateral views.

The differences observed in the clinical cases also confirm the results of other studies from the specialized literature, previously being reported that the response to the treatment depends on the degree of extension of the pain and the expression of its related phenomena, being a different response to the treatment observed, with less efficiency in people with TMD and widespread multi-site pain. Identification of these patients is considered to be insightful at the early stage of clinical examination and diagnosis, to identify factors that may have a negative impact on treatment outcomes, and also to establish realistic treatment expectations.

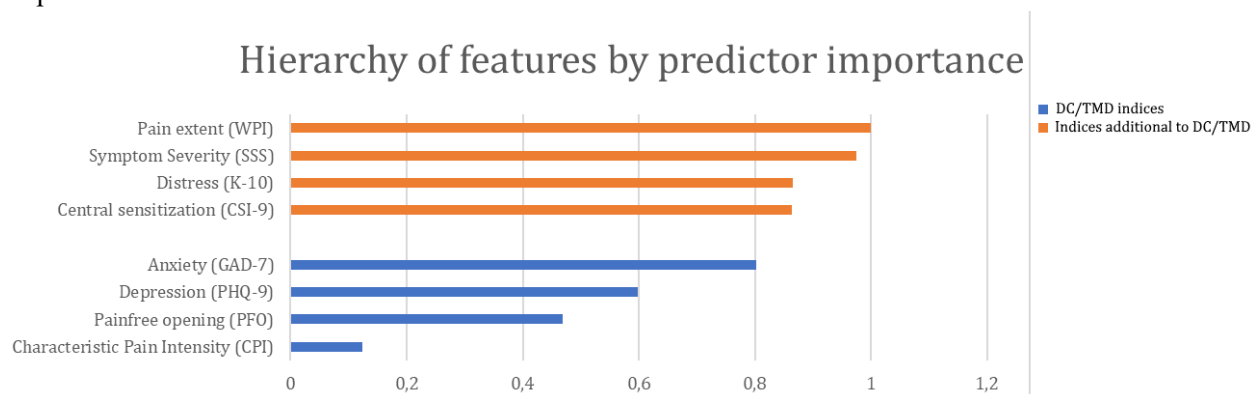


Figure 3.3. Hierarchical plot of predictor importance for the features used in clustering

We performed an analysis of the importance as predictors (the ability to separate per cluster) for the clinical characteristics (*features*) used to identify the 2 clusters (Figure 3.3), observing a greater separating ability of the additional indices to the DC/TMD protocol in comparison of the protocol. The most important predictors are represented by the composite index of *fibromyalginess* – FSDC, based on summation of the *widespread pain index* (WPI) and the *symptom severity score* (SSS) for disorders associated with widespread pain, and at the opposite extreme, with lower importance scores as predictors are the *pain-free opening size* and the *characteristic pain intensity* (CPI).

4. EXTENSION OF DISORDERS ASSOCIATED WITH MASTICATORY MUSCLE DYSFUNCTION

4.1. Extent of pain in patients with masticatory muscle dysfunction

Currently, in the specialized literature, the masticatory muscle dysfunctions, along with other pathologies (fibromyalgia, tension headache, etc.) are approached regarding the aspects of clinical manifestation, intensity and evolution as potential clinical variants of the central sensitization syndrome [25], which involves an interdisciplinary approach to diagnosis and treatment. The concept of fibromyalginess was introduced in 2010 by Prof. Frederick Wolfe, to describe and quantify the polysymptomatic distress (fatigue, somatic symptoms, cognitive problems, sleep disorders, decreased mechanical pain sensitivity, etc.), felt by patients with different pain syndromes. The Polysymptomatic Distress Scale (PSD/FSDC) indicates the degree of fibromyalginess (FMS), regardless of the presence/confirmation of the diagnosis of fibromyalgia, by measuring the extent and severity of symptoms, based on the summation of the extent of pain in the body (WPI – widespread pain index) and its associated symptoms (SSS – symptom severity scale) [26].

Patients with masticatory muscle dysfunction in the study sample were divided based on the absence/presence of a clinically relevant level of fibromyalginess (FMS) into 2 subgroups: no FMS (NFM, n = 35, FSDC score < 13) and presence of FMS (FM, n = 20, FSDC score ≥ 13). In the NFM and FM groups there were subjects, both with myogenous and myogenous-arthrogenous clinical variants, as well as with acute and chronic phases of masticatory muscle dysfunction, noting that with the presence of a clinically relevant level of *fibromyalginess*, a predominance is attested of clinical cases with myogenous-arthrogenous variant and chronic phase, these trends being statistically significant ($p_{CA} = 0.006$,

respectively $p_{CA} = 0.03$). Based on the scores for the components of the FSDC scale, patients in the NFM and FM groups showed a number of differences. For most anatomical sites in the WPI scale, higher frequencies of the presence of pain are attested with the presence of FMS, with statistically significant trends (except for lower limb segments – forearm and calves).

Table 4.1. Mean values of descriptive clinical indices (DC/TMD protocol, additional indices) in masticatory muscle dysfunction versus absence/presence of fibromyalgia

Indices	Patients with MMD			<i>p</i>
	TG (N = 55)	NFM (n = 35)	FM (n = 20)	
		1	2	<i>Trend 2 vs 1</i>
DC/TMD indices				
<i>Overjet</i>	2.72 (0.17)	2.60 (0.19)	2.92 (0.36)	0.433↔
<i>Overbite</i>	4.89 (0.32)	4.22 (0.32)	6.05 (0.60)	0.007 ↑
<i>MDV</i>	0.95 (0.09)	0.97 (0.13)	0.92 (0.12)	0.800↔
<i>PFO</i>	33.4 (1.31)	35.77 (1.60)	29.35 (2.02)	0.009 ↓
<i>PO</i>	46.1 (0.88)	47.37 (0.97)	43.75 (1.63)	0.033 ↓
<i>AO</i>	50.3 (0.84)	50.77 (0.92)	49.35 (1.69)	0.468↔
<i>RL</i>	10.9 (0.41)	10.55 (0.51)	11.40 (0.71)	0.342↔
<i>LL</i>	9.91 (0.29)	9.90 (0.36)	9.92 (0.50)	0.968↔
<i>PR</i>	7.62 (0.29)	7.65 (0.34)	7.55 (0.57)	0.874↔
<i>JFLS</i>	1.60 (0.23)	0.89 (0.16)	2.83 (0.46)	<.001 ↑
<i>GCPS₁</i>	3.33 (0.37)	2.74 (0.49)	4.35 (0.46)	0.011 ↑
<i>GCPS₂</i>	5.91 (0.33)	5.51 (0.43)	6.60 (0.46)	0.048 ↑
<i>GCPS₃</i>	4.09 (0.24)	3.65 (0.26)	4.85 (0.46)	0.017 ↑
<i>CPI</i>	44.4 (2.73)	39.71 (3.45)	52.66 (3.90)	0.008 ↑
Additional indices to the DC/TMD protocol				
<i>MMI</i>	2.64 (0.32)	2.14 (0.37)	3.50 (0.56)	0.027 ↑
<i>Di</i>	16.2 (0.61)	14.88 (0.84)	18.40 (0.56)	<.001 ↑
<i>TMI_F</i>	0.39 (0.02)	0.33 (0.02)	0.50 (0.04)	<.001 ↑
<i>TMI_M</i>	0.67 (0.02)	0.61 (0.03)	0.78 (0.03)	<.001 ↑
<i>TMI_A</i>	0.40 (0.03)	0.31 (0.04)	0.55 (0.05)	<.001 ↑
<i>TMI</i>	0.49 (0.02)	0.42 (0.02)	0.61 (0.03)	<.001 ↑
<i>TOI</i>	4.46 (0.41)	3.52 (0.33)	6.08 (0.89)	0.006 ↑
<i>MVAS</i>	6.67 (0.22)	6.82 (0.29)	6.40 (0.32)	0.336↔
<i>VOH</i>	0.21 (0.01)	0.23 (0.02)	0.18 (0.02)	0.226↔
<i>DM_{SSI}</i>	2.24 (0.13)	1.74 (0.10)	3.10 (0.22)	<.001 ↑
<i>DA_{SSI}</i>	1.62 (0.21)	1.05 (0.24)	2.60 (0.27)	<.001 ↑
<i>FM_{SSI}</i>	2.25 (0.14)	1.97 (0.15)	2.75 (0.25)	0.006 ↑
<i>FA_{SSI}</i>	1.22 (0.19)	1.08 (0.27)	1.45 (0.24)	0.162↔

Note: Values are presented as mean (standard error); ↓ – the mean values in NFM group are lower than those in FM group; ↑ – the mean values in NFM group are higher than those in FM group; ↔ – non-significant differences between means. Abbreviations: NFM – the absence of a clinically relevant level of fibromyalginess; FM – the presence of fibromyalginess (FMS); MDV – midline deviation; PFO – pain-free opening; PO – passive opening; AO – active opening; RL – right laterotrusion; LL – left laterotrusion; PR – protrusion; JFLS – jaw functional limitation scale; GCPS₁ – current pain intensity; GCPS₂ – mean pain intensity; GCPS₃ – maximum pain intensity; CPI – characteristic pain intensity; MMI - mandibular mobility index; Di - Helkimo Dysfunctional Index; TMI_F - Functional TMI Subscale; TMI_M - Muscular TMI Subscale; TMI_A - Articular TMI Subscale; TMI - Temporomandibular Index; TOI - Temporomandibular Opening Index; MVAS - self-perceived masticatory performance (VAS); VOH - variance of hue; DM_{SSI} - Duration of myalgia (SSI Subscale); DA_{SSI} - Duration of arthralgia (SSI Subscale); FM_{SSI} - Frequency of myalgia (SSI Subscale); FA_{SSI} - Frequency of arthralgia (SSI Subscale); Statistical analysis used: Welch's t-test (p_w).

For the Symptom Severity Scale (SSS), it is observed that in the NFM group, there is a predomination of patients with *missing problems/mild problems* for the symptoms of fatigue, insufficient sleep and cognitive impairment (ability to focus/memory), while in the FM group – there is a predomination of more severe variants (*moderate problems/severe problems*), the differences being statistically significant ($p < 0.001$). In the FM group, there were statistically significantly higher frequencies for the presence of abdominal cramps, depressive states and headaches compared to the NFM group. The total fibromyalgia score – FSDC, as well as the WPI and SSS total scores, showed statistically significantly higher values in the FM group compared to the NFM.

We analyzed the expression peculiarities (intensity) for quantitative clinical indices, descriptors of the clinical manifestations of masticatory muscle dysfunction (indices from the DC/TMD protocol and additional indices) versus the absence/presence of fibromyalgia (FMS) criterion (Table 4.1).

For the indices of the DC/TMD protocol, with the presence of fibromyalginess (FMS), there was observed a differentiated behavior of the parameters, with a significant increase (overbite, functional limitation, GCPS/CPI pain indices) and significant decrease (pain-free opening, passive opening) for the mean values. A series of indices (overjet, midline deviation, amplitudes of active opening and eccentric movements) did not demonstrate significant differences between groups. For additional indices to the DC/TMD protocol, with the presence of FMS, a significant increase is observed in a series of indices (mandibular mobility, severity indices and their subscales, end-feel index, frequency and duration of myalgia, duration of arthralgia). Subjective and objective indices of masticatory performance and arthralgia frequency index did not demonstrate statistically significant differences between groups. The ratio between active and passive opening (TOI, *end feel*) increases significantly, this is due to the significant decrease of the passive opening component, which has statistically significantly lower values in the FM group compared to the NFM.

4.2. Indices of sensory function in different clinical subtypes of masticatory muscle dysfunction

Pain is a subjective phenomenon with an extended spectrum of clinical manifestation in patients with masticatory muscle dysfunction (MMD). The investigation of somatosensory profiles in patients with MMD is a current active direction in research, there is currently no consensus on how the sensitivity to noxious stimuli changes in these patients, as well as in which clinical subtypes of MMD there is an increase/decrease in the sensitivity of the somatosensory system [2].

Summing up the results when evaluating the subjective and objective indices of sensory sensitivity reveals that for objective indices of quantitative-sensory testing (QST), the *disease phase* criterion shows the most obvious influence on them, followed by the *presence/absence of fibromyalginess* (FMS) criterion and the *myogenous/myogenous-arthrogenous clinical variant* criterion. For the subjective indices of sensory sensitivity (SHS), the most obvious influence on the behavior of the indices is achieved by the *presence/absence of FMS* criterion, followed by the *phase of the disease* and the *clinical variant*.

In the specialized literature, the problem of studying the spatial characteristics of muscle hyperalgesia is a current issue, given that previously it was observed that the masticatory muscles (masseter, temporalis) would present a sensory, morphological, histological and physiological partitioning. The implications of this fact are due to the fact that the data obtained during the standard clinical examination by palpation are not considered optimal, previously, methods were proposed with the standardized algometric assessment of mechanical pain sensitivity (MPS) at the level of masticatory muscles, with the creation of muscle pain maps. The degree of diversity and inhomogeneity of sensitivity to mechanical stimuli (pressure/palpation) requires the study of new descriptors, this having clinical implications at the diagnostic level, in order to improve the currently used tools for muscle sensitivity assessment.

We investigated the particularities of *mechanical pain sensitivity* at the masseter muscle level in patients with masticatory muscle dysfunction ($n = 30$) versus the control group ($n = 30$), composed of women, in whom the presence of MMD was excluded following the clinical examination according to the DC/TMD protocol.

Table 4.2. Direction of changes in objective and subjective indices of sensory function in clinical subtypes of masticatory muscle dysfunction

Indices/Examined sites				Clinical subtypes criteria		
				Chronification (Acute → Chronic)	Local extension (Myogenous → Myogenous-arthrogenous)	Systemic expansion (non-FMS → fibromyalginess)
Objective Quantitative Sensory Testing (QST) indices	Mechanical stimulation by pressure	Hypothenar region	PPT			
			PTT			
			PPE			↓
		Masseter	PPT	↓	↓	↓
			PTT			
			PPE			
		TMJ	PPT	↓		↓
			PTT	↓		
			PPE			
	Vibrotactile stimulation	Forearm	↑	↑	↑	
		Masseter	↑			
		TMJ	↑	↑	↑	
	Mean tactile sensitivity (MTS) – masseter projection			↑		
Subjective sensory indices	Total sensory sensitivity (SHS)		↑		↑	
	Allergy (SHS)					
	Heat (SHS)					
	Cold (SHS)		↑		↑	
	Light (SHS)		↑			
	Pain (SHS)			↑	↑	
	Smell (SHS)				↑	
	Hearing (SHS)		↑			
	Taste (SHS)				↑	
Tactile (SHS)				↑		

Note: Direction of statistically significant changes: ↓ – reduction (decrease); ↑ – increase.

We investigated the ability of the H_{rel} index and other indices (COG-DC, S, σ) in the clinical differentiation of individuals with MDD from non-cases (healthy controls) (Table 4.3). The parameters COG-DC, σ and H_{rel} can statistically significantly differentiate MDD cases from non-cases based on the studied sample ($p < 0.0001$), and statistically non-significant trends are observed for the Shannon entropy (S). The diagnostic performance of the indicators (AUC value) is in the following hierarchical order: relative heterogeneity (0.991) > standard deviation (0.929) > COG distance from the center (0.851) > Shannon entropy (0.629), the values being considered as very excellent (AUC > 0.9) for H_{rel} ; excellent (AUC = 0.8-0.9) for COG-DC and σ ; weak for S (AUC = 0.5-0.6). The diagnostic effectiveness (Youden index – J) reveals that COG-DC, σ and H_{rel} have values that allow the detection of cases versus non-cases ($J > 0.5$), while S has an insufficient value. The hierarchy of diagnostic efficiency (J, Se/Sp) in descending order is: relative heterogeneity (0.9667, 100/96.67) > standard deviation (0.8000, 96.77/83.33) > COG distance to center (0.6000, 73.33/86.67) > Shannon entropy (S) (0.2667, 73.33/53.33).

We performed the comparative analysis of ROC curves for the developed parameter H_{rel} versus COG-DC, σ , S for assessing their capacity at differentiating people with MMD from non-cases (healthy controls). The relative heterogeneity parameter demonstrates a more pronounced ROC curve against the Shannon entropy (area difference – 0.362; $z = 5.162$; $p < 0.0001$), followed by the COG distance from the

center (area difference – 0.140; $z = 3.083$; $p = 0.0020$) and standard deviation (area difference – 0.0622; $z = 2.195$; $p < 0.0282$). The observed differences reveal that the index of relative heterogeneity (H_{rel}) represents an integrative index with a high diagnostic efficacy and performance (identifying and differentiating cases from non-cases) with a high sensitivity and specificity (100/96.67%), which it allows both the evaluation of the diversity of the pain map and the quantification of the data differences in regard to the average PPT value.

Table 4.3. Descriptive indices of mechanical pain sensitivity (MPS) in patients with masticatory muscle dysfunctions (MMD) versus healthy controls

MPS indices	MPS parameters	MMD patients (n = 30)	Healthy controls (n = 30)	p_w
		1	2	1 vs 2
Centrality indices (COG)	x	1.9978 (0.006)	1.9975 (0.002)	0.958
	y	2.0312 (0.009)	1.9993 (0.004)	0.003
	COG distance from the center (COG-DC)	0.0588 (0.005)	0.0213 (0.002)	< 0.001
	Angle (COG-A)	133.0591 (15.813)	168.7605 (16.098)	0.119
PPT indices	Mean value	0.9014 (0.033)	1.4280 (0.014)	< 0.001
	Maximum value	1.1287 (0.038)	1.5483 (0.018)	< 0.001
	Minimum value	0.6813 (0.028)	1.3127 (0.017)	< 0.001
Pain map diversity indices	Standard deviation (σ)	0.1485 (0.009)	0.0736 (0.005)	< 0.001
	Shannon Entropy (S)	1.7551 (0.036)	1.6838 (0.035)	0.167
	Relative heterogeneity (H_{rel})	0.2979 (0.022)	0.0870 (0.006)	< 0.001
Spatial impairment	Affected surface, %	72.5926 (5.320)	0.0000 (0.000)	< 0.001

Note: data are presented as mean (standard error); statistical analysis – Welch’s t-test

Table 4.4. ROC indices for the descriptive parameters of the diversity of the MPS spatial distribution

ROC Indices	COG distance from the center (COG-DC)	Standard deviation (σ)	Shannon Entropy (S)	Relative Heterogeneity (H_{rel})
AUC (area under curve) parameters				
AUC	0,851	0,929	0,629	0,991
Standard error*	0,0494	0,0343	0,0730	0,00952
CI95%•	0,736-0,930	0,832-0,979	0,494-0,750	0,924-1,000
CI95%#	0,744-0,928	0,812-0,974	0,473-0,756	0,939-1,000
z	7,100	12,513	1,766	51,589
p	<0,0001	<0,0001	0,0773	<0,0001
Youden index parameters				
Youden index (J)	0,6000	0,8000	0,2667	0,9667
CI95%#	0,3667-0,733	0,5667-0,9000	0,1265-0,4000	0,7800-1,0000
Sensitivity, %	73,33	96,67	73,33	100
Specificity, %	86,67	83,33	53,33	96,67

Note: * – calculation of the standard error according to Hanley&McNeil (1982); • – confidence interval based on exact binomial testing; # – confidence interval based on bootstrap technique (1000 iterations, random number seed – 978); z – statistical value of z ; p – level of significance (Area=0.5).

In the specialized literature, a current research issue is establishing the influence of various factors on the change of quantitative sensory indices to mechanical stimuli, especially regarding the influence of stress. In the study, it was evaluated how the indices of mechanical sensitivity to pressure (PPT, PTT, PPE)

change under the influence of operational stress, experimentally modeled by means of the Stress Tolerance Test (Skytest, Germany), under standardized test conditions. Testing the hypothesis that baseline values (pre-stress) decreased after the operational stress (post-stress state) ($\mu_{\text{pre-stress}} - \mu_{\text{post-stress}} > 0$), revealed for the total group (TG, n = 55) trends of a statistically significant decrease for the pain tolerance threshold (PTT) of the masseter muscle (p = 0.002), the pressure pain endurance index (PPE) of the masseter muscle (p = 0.003), which would indicate a certain degree of post-stress hypo-algesia in people with masticatory muscle dysfunctions (Table 4.5). Testing of the alternative hypothesis, according to which the initial values (pre-stress) increased after the operational stress (post-stress) ($\mu_{\text{pre-stress}} - \mu_{\text{post-stress}} < 0$), did not identify statistically significant changes of the pairs of indices.

Table 4.5. Change in the values of mechanical pain sensitivity (MPS) indices in patients with masticatory muscle dysfunctions (N = 55) before and after operational stress modelling

QST values (pre-stress vs. post-stress)	W (Wilcoxon)	p	MD	SED	Effect size (Biserial rank correlation)
PPT_{Masseter}	683 ^a	0.699	-0.0200	0.0510	-0.0808
PTT_{Masseter}	1111	0.002	0.1397	0.0502	0.4422
PPE_{Masseter}	1103	0.003	0.1950	0.0677	0.4318
$PPT_{\text{T MJ}}$	699	0.725	-0.0400	0.0624	-0.0922
$PTT_{\text{T MJ}}$	858	0.232	0.0400	0.1126	0.1143
$PPE_{\text{T MJ}}$	835 ^a	0.215	0.1250	0.1196	0.1239

Note: statistical analysis used: *t paired samples test, Wilcoxon rank; hypothesis tested* – $\mu_{\text{pre-stress}} - \mu_{\text{post-stress}} > 0$; ^a 1 pair contained equal values. MD – mean difference; DES – standard error difference.

4.3. Clinical subtypes of masticatory muscle dysfunction and psycho-emotional stress (DC/TMD Axis II/additional psycho-emotional indices)

The current evaluation of masticatory muscle dysfunctions is carried out according to the biopsychosocial approach of the given pathology, with the evaluation of the somatic clinical manifestations (Axis I – clinical examination) and the psychosocial aspects (Axis II) associated to the pain disorder [6].

Preliminarily, we analyzed the correlations between the indices associated with Axis I (clinical stomatognathic indices) and those associated with Axis II (psycho-emotional state indices), revealing the following relationships: the mandibular mobility index (MMI) correlates *positively* with the number of traumatic events – NTE (r = 0.417, p = 0.002), number of acute stress disorders – NASD (r = 0.404, p = 0.002), anxiety – ANX (r = 0.316, p = 0.019) and *negatively* with the age of the first traumatic event – AFTE (r = -0.313, p = 0.020); The dysfunction severity index (Di) correlates *positively* with NTE (r = 0.423, p = 0.001), NASD (r = 0.358, p = 0.007), ANX (r = 0.289, p = 0.032); the number of affected muscle sites (NAMS) correlates *positively* with ANX (r = 0.307, p = 0.023) and *negatively* with AFTE (r = -0.378, p = 0.004); the temporomandibular index (TMI) correlates *positively* with stress-tolerance – STO (r = 0.280, p = 0.039), depression – DEP (r = 0.306, p = 0.023) and *negatively* with AFTE (r = -0.351, p = 0.009); the end-feel index (TOI) correlates *positively* with DEP (r = 0.267, p = 0.049); the objective index of masticatory performance (VoH) correlates *negatively* with the current stress intensity – STR (r = -0.304, p = 0.024) and ANX (r = -0.365, p = 0.006); the duration of muscle pain correlates *positively* with NET (r = 0.267, p = 0.049), ANX (r = 0.369, p = 0.006), DEP (r = 0.369, p = 0.006); the characteristic pain intensity (CPI) in the stomatognathic system correlates *positively* with STR (r = 0.284, p = 0.036).

Subsequent, we analyzed the intensity of the expression of psychoemotional state indices according to the clinical subtypes of masticatory muscle dysfunctions (Table 4.6). DC/TMD Axis II instrument indices (ANX, DEP) demonstrated statistically significantly higher values with the presence of fibromyalginess and the chronic phase of the disease, but no statistically significant differences were observed for indices of past traumatic events and for the operational stress intensity. The mean value of stress-tolerance was

statistically significantly higher in the acute group than in the chronic group. Depending on the myogenous/myogenous-arthrogenous clinical variant, various modification trends for the indices were observed, but without statistical significance.

In patients with masticatory muscle dysfunctions, the intensity of expression of anxiety and depression are inter-correlated ($r = 0.762$, $p < 0.001$). For dental clinical practice, in the *screening* of psycho-emotional disorders, it is important to identify the critical scores (which may need additional investigations/specialist consultation) regarding the DC/TMD Axis II instruments (GAD-7 – anxiety, PHQ-9 – depression), for which there are established reference values for differentiating the levels of high intensity expression (HI – *high intensity*) from those of low intensity expression (LI – *low intensity*). We analyzed the combinations between levels of anxiety and depression of different intensity depending on the clinical subtypes of masticatory muscle dysfunctions (figure 4.1).

In the total group of patients with masticatory muscle dysfunctions ($N = 55$), the following combinations of intensity levels of anxiety and depression are attested, arranged hierarchically in order of decreasing frequency: *Low Intensity Anxiety-Low Intensity Depression* (56.4%); *Low Intensity Anxiety-High Intensity Depression* (18.2%), *High Intensity Anxiety – High Intensity Depression* (14.5%), *High Intensity Anxiety – Low Intensity Depression* (10.9%).

Table 4.6. Expression of indices of psychoemotional state in clinical subtypes of masticatory muscle dysfunction

Indices of psycho-emotional state/ stress	TG (N=55)	NFM (n=35)	FM (n=20)	p_w	M (n=26)	MA (n=29)	p_w	AD (n=31)	CD (n=24)	p_w
		1	2	2 vs 1	3	4	4 vs 3	5	6	5 vs 6
DC/TMD indices (Axis II)										
Anxiety (ANX)	7.62 (0.68)	6.06 (0.80)	10.35 (1.00)	< .001↑	7.19 (0.85)	8.00 (1.05)	0.278↔	6.35 (0.80)	9.25 (1.11)	0.020↑
Depression (DEP)	7.02 (0.64)	5.34 (0.64)	9.95 (1.10)	< .001↑	5.96 (0.78)	7.97 (0.98)	0.058↔	5.71 (0.87)	8.71 (0.85)	0.009↑
Indications of past stress/traumatic events										
Number of traumatic events (NTE)	7.11 (1.06)	6.20 (1.31)	8.70 (1.78)	0.266↔	6.42 (1.61)	7.72 (1.41)	0.274↔	5.84 (1.54)	8.75 (1.36)	0.081↔
Number of acute stress disorders (NASD)	3.87 (0.81)	3.71 (1.18)	4.15 (0.92)	0.772↔	4.04 (1.58)	3.72 (0.66)	0.572↔	3.58 (1.29)	4.25 (0.87)	0.335↔
Age of first traumatic event (AFTE)	13.2 (0.73)	13.43 (0.81)	12.80 (1.46)	0.710↔	13.23 (0.95)	13.17 (1.12)	0.516↔	13.84 (0.98)	12.38 (1.10)	0.836↔
Indices of operational stress (modeled experimentally)										
Operational stress intensity – VAS (STR)	3.22 (0.27)	3.00 (0.38)	3.60 (0.36)	0.261↔	3.15 (0.46)	3.28 (0.32)	0.415↔	2.87 (0.38)	3.67 (0.38)	0.075↔
Stress tolerance (STO), %	79.8 (0.14)	79.65 (0.17)	80.02 (0.25)	0.245↔	79.80 (0.14)	79.76 (0.24)	0.558↔	80.09 (0.15)	79.38 (0.24)	0,010↓

Note: TG – the total group; NFM – the absence of a clinically relevant level of fibromyalginess; FM – the presence of fibromyalginess (FMS); AD – acute disorders; CD – chronic disorders. Values are presented as mean (standard error); ↓ – the mean values in group 2/4/6 are significantly lower than those in group 1/3/5; ↑ – the mean values in group 2/4/6 are significantly higher than those in group 1/3/5; ↔ – non-significant differences between means. Statistical analysis used: Welch’s t-test

According to the criteria for differentiating the clinical subtypes of masticatory muscle dysfunctions (MMD), statistically significant differences are observed ($p_F = 0.045$, Fischer's exact test) of distribution of proportions, with the following ranking of combinations of different intensity of anxiety and depression (arranged hierarchically, in decreasing order of frequency):

- *Absence/presence of fibromyalginess (FMS) criterion:* in the NFM group the combination ANX-LI – DEP-LI (74.3%) predominates, followed by ANX-HI – DEP-LI (11.4%); ANX-HI – DEP-HI (8.6%) and ANX-LI – DEP-HI (5.7%); while in the FM group a proportionally more balanced distribution is observed, the 4 types of combinations having almost similar frequencies (20-30 %);
- *Clinical variant criterion:* in the myogenous group (M), the combination ANX-LI – DEP-LI (61.5%) predominates, followed by ANX-HI – DEP-LI (23.1%) and equal frequencies for ANX-LI – DEP-LI and ANX-LI – DEP-LI (7.7%); while in the myogenous-arthrogenous group (MA), there is also a predomination of ANX-LI – DEP-LI (51.7%), but in this case, it is followed by ANX-HI – DEP-HI (20.7%) and in equal frequencies by ANX-LI – DEP-HI and ANX-HI – DEP-LI (13.8%);
- *Phase of the disease criterion:* in the acute disorders (AD) group, the combination ANX-LI – DEP-LI (77.4%) predominates, followed by ANX-HI – DEP-HI (16.1%) and ANX-HI – DEP-LI (6.5%), no cases were registered with the ANX-LI – DEP-HI combination (0%); while in the chronic disorders (CD) group there are approximately equal frequencies for the combinations ANX-HI – DEP-LI (33.8%), ANX-LI – DEP-LI (29.2%) and ANX-LI – DEP-HI (25%) and fewer cases with the combination ANX-HI – DEP-HI (12.5%).

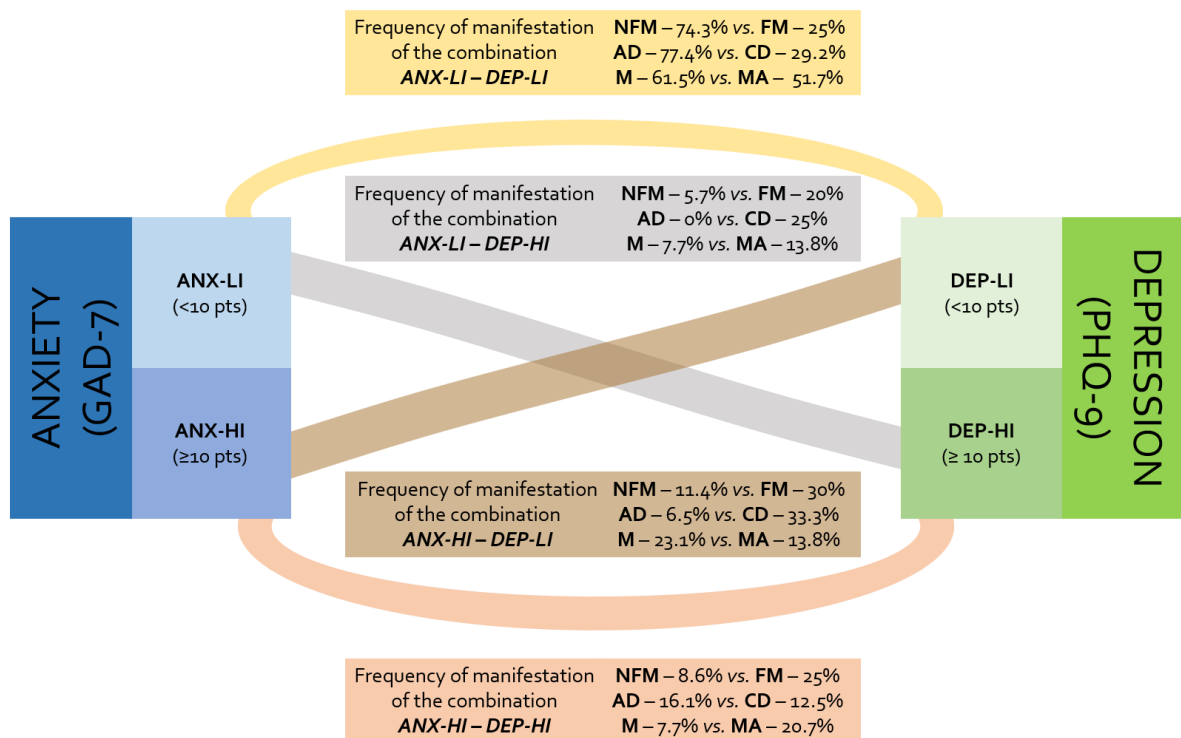


Figure 4.1. Combinations of different intensity levels of anxiety and depression in different clinical subtypes of masticatory muscle dysfunction

It was observed that in some clinical subtypes (*absence of fibromyalginess, acute disorders and myogenous variant*), the *LI* level combination for anxiety and depression predominates, the proportions between the combination variants being statistically significantly different for the NFM group (Fisher exact test, $p_F = 0.044$) and the acute disorders group ($p_F < 0.001$); in other clinical subtypes, no statistically significant differences were observed.

GENERAL CONCLUSIONS

1. In patients with masticatory muscle dysfunctions, based on the DC/TMD protocol and additional indices, different variants of association of local, regional, systemic disorders are observed, which determine the structure, severity and extent of the disease. In the polymorphism of stomatognathic manifestations of masticatory muscle dysfunctions, four groups of disorders were highlighted: a) disorders characteristic of the clinical form (myogenous/myogenous-arthrogenous); b) disorders characteristic to the phase of the disease (acute/chronic); c) significant irregularities for both criteria (clinical form, disease phase); d) common stomatognathic disorders in different clinical subtypes. The mathematical-statistical analysis revealed 2 distinct clinical patterns – regional-localized/regional-generalized disorders.
2. In patients with masticatory muscle dysfunctions, for the highlighting of the clinical subtypes (myogenous/myogenous-arthrogenous, acute and chronic, absence/presence of fibromyalginess), it is useful to determine the mechanical quantitative-sensory indices (QST) that change statistically significantly depending on the manifestations of the disease. In patients with masticatory muscle dysfunctions, total sensory hypersensitivity, as well as its subscales, manifest more clearly in the following order of decrease: generalization of disorders (fibromyalginess) > chronicity of the disease > TMJ involvement in the pathology of masticatory muscle dysfunctions.
3. The expression of indices of the psycho-emotional state is varied in patients with masticatory muscle dysfunctions, with statistically significantly higher values of the intensity of anxiety and depression and with trends of more severe changes in the indices of traumatic events from the past and operational stress in the several clinical MMD subtypes (chronic, myogenous-arthrogenous, presence of fibromyalginess); the impact of operational stress on the mechanical pain sensitivity in the stomatognathic system is mainly expressed by reducing the pressure tolerance and endurance of the masseter muscle.
4. Masticatory performance (two-color chewing gum test) is statistically significantly lower in patients with the chronic phase of masticatory muscle dysfunction; in subjects with the myogenous and acute variants, there was observed a significant tendency of increased frequency of overestimation of one's own masticatory performance during self-assessment when compared to the clinically determined level (masticatory performance class).
5. A new integral parameter (relative heterogeneity) was developed for the qualitative-quantitative description of the spatial distribution of mechanical pain sensitivity in the projection of the masseter muscle, with high diagnostic efficacy and performance.

PRACTICAL RECOMMENDATIONS

1. In case of plurimorphic clinical manifestation of masticatory muscle dysfunction, it is recommended to supplement the DC/TMD protocol with additional indicators (severity of dysfunctions, duration and frequency of symptoms, extent of pain, indicators of mechanical pain sensitivity, sensory sensitivity, indicators of past traumatic events), with the identification of the level of chronicity and generalization of the disorders.
2. In all variants of masticatory muscle dysfunction, treatment methods with local and regional effect are indicated; in the generalized subtype, methods with a systemic effect are also to be associated.
3. For the objective characterization of local pain in the projection of the masseter muscle, it is may prove to be informative to conduct a pain pressure threshold mapping in a 3x3 format at the masseter muscle, with the assessment of the degree of diversity and inhomogeneity of mechanical pain sensitivity based on the integral parameter – *relative heterogeneity* (Patent MD 1608 Y BOPI no. 3/2022).
4. In patients with masticatory muscle dysfunction, it is recommended to conduct a simultaneous analysis of the subjective and objective indices of masticatory performance by testing the mixing ability (two-color chewing gum test) with the determination of: the subjective clinical class of masticatory performance, the patient's self-assessment; the objective index VoH (variance of hue).
5. The monitoring of patients with different clinical subtypes of masticatory muscle dysfunction can be improved and individualized by applying additional mechanical quantitative-sensory indices (PPT, PTT; PPE) and dynamic QST indices (pain intensity upon vibrotactile stimulation) in the projection of the structures of the stomatognathic system (masseter muscle, TMJ) and standardized reference sites.
6. In patients with masticatory muscle dysfunctions, the application of the Sensory Hypersensitivity Scale allows the complex monitoring of this category of patients with the highlighting of the associated sensory disturbances, which can aggravate the clinical picture.

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ADNOTARE
Bordeniuc Gheorghe
„Indici clinico-fiziologici în disfuncția mușchilor masticatori”
Teză de doctor în științe medicale, Chișinău, 2023

Structura tezei. Textul tezei este expus pe 120 pagini text de bază, procesate la calculator, fiind constituită din: lista abrevierilor, introducere, 5 capitole, concluzii generale, recomandări practice, bibliografia din 288 surse și 4 anexe. Materialul ilustrativ include 23 tabele, 15 figuri și 7 formule.
Cuvinte-cheie: dereglări temporomandibulare, disfuncții a mușchilor masticatori, indici clinico-fiziologici, diagnostic.

Domeniul de studiu: 323.01 – Stomatologie.

Scopul lucrării: Studierea particularităților disfuncțiilor mușchilor masticatori (varianta clinică, faza bolii) în baza suplínirii protocolului DC/TMD cu indici clinico-fiziologici locali, regionali și sistemici.

Obiectivele cercetării: Studierea activității sistemului stomatognat la pacienți cu disfuncții a mușchilor masticatori în funcție de faza bolii și varianta clinică. Evidențierea în baza analizei matematico-statistice a tiparelor distincte ale dereglărilor mușchilor masticatori în baza indicilor clinico-fiziologici locali, regionali, sistemici și potențialul impact terapeutic al gutierelor ocluzale în reabilitarea funcționalității sistemului stomatognat. Studierea particularităților dereglărilor generalizate în cadrul subtipurilor clinice ale disfuncției mușchilor masticatori. Studierea performanței masticatorii în baza indicilor subiectivi și obiectivi în diferite subtipuri clinice ale disfuncției mușchilor masticatori. Elaborarea parametrilor integrali de apreciere a manifestărilor algice în sistemul stomatognat la pacienți cu disfuncții ale mușchilor masticatori.

Noutatea și originalitatea științifică: În premieră, au fost evidențiați indicii activității sistemului stomatognat, statistic semnificativ asociați cu varianta clinică a disfuncției mușchilor masticatori, faza bolii și indicii comuni ambelor criterii. Pentru prima dată, în baza analizei matematico-statistice, au fost identificate manifestările clinice, care diferențiază pacienții cu disfuncții ale mușchilor masticatori în 2 tipare distincte (regională, regional-generalizată) în baza extinderii și severității dereglărilor. Structura și severitatea indicilor cantitativi și calitativi ai disfuncțiilor mușchilor masticatori sunt în dependență de fenomenul de *fibromyalginess*. Aprecierea funcției masticatorii necesită evaluarea concomitentă a indicilor obiectivi și subiectivi, care descriu aspecte diferite ale performanței masticatorii la pacienți cu disfuncții ale mușchilor masticatori. Pentru prima dată, a fost demonstrat că hipersensibilitatea senzorială este un criteriu informativ, caracteristic subtipurilor clinice de disfuncții ale mușchilor masticatori. Pentru prima dată, s-a propus metoda de cartografiere a mușchiului maseter cu aprecierea indicelui de *heterogenitate relativă* a hărții algice, care permite o abordare nouă și informativă a disfuncțiilor mușchilor masticatori. Pentru prima dată, s-a demonstrat că modelarea stresului operațional permite evidențierea modificării toleranței și rezistenței algice a mușchiului maseter, care nu se modifică esențial în condiții de confort relativ la pacienții cu disfuncții ale mușchilor masticatori, fapt care evidențiază anumite particularități ale conexiunii stresului și a manifestărilor locale ale durerii.

Importanța practică: Structura tabloului clinic și expresia indicilor clinico-fiziologici a disfuncției mușchilor masticatori depinde de varianta clinică, faza bolii și prezența generalizării simptomelor. Aprecierea diferențiată a funcției masticatorii se poate realiza prin indici subiectivi și obiectivi la aplicarea testului de apreciere a abilității de mixare la pacienții cu disfuncții ale mușchilor masticatori. Personalizarea diagnosticului disfuncțiilor mușchilor masticatori în funcție de faza bolii, varianta clinică se poate realiza în baza indicilor hipersensibilității senzoriale. A fost determinată valoarea diagnostică a modelării experimentale a stresului operațional și impactul acestuia asupra indicilor cantitativ-senzoriali la pacienți cu disfuncții ale mușchilor masticatori. În premieră, a fost elaborată tehnologia de examinare loco-regională a durerii, prin analiza heterogenității distribuției spațiale a sensibilității mecanice algice a mușchiului maseter.

Implementarea rezultatelor științifice. Rezultatele cercetărilor științifice au fost implementate în procesul de cercetare, activitate metodologică și clinică în Clinica stomatologică Fala Dental, Clinica stomatologică Megalux Dent, IM Centrul Stomatologic Municipal, în procesul didactic de instruire la Catedra de Stomatologie terapeutică a USMF ”Nicolae Testemițanu”.

АННОТАЦИЯ

Борденюк Георгий

„Клинико-физиологические показатели при дисфункции жевательных мышц“
Докторская диссертация в области медицинских наук, Кишинев, 2023

Структура диссертации. Текст диссертации представлен на 120 основных текстовых страницах, обработанных на компьютере и состоящих из: списка сокращений, введения, 5 глав, общих выводов, практических рекомендаций, библиографии из 288 источников и 4 приложений. Иллюстративный материал включает 23 таблицы, 15 рисунков и 7 формул. **Ключевые слова:** височно-нижнечелюстные расстройства, дисфункции жевательных мышц, клинико-физиологические показатели, диагностика.

Область изучения: 323.01 – Стоматология.

Цель работы: Изучение особенностей дисфункций жевательных мышц (клинический вариант, фаза заболевания) на основе пополнения протокола DC/TMD с локальными, региональными и системными клинико-физиологическими показателями.

Научно-исследовательские цели: Изучение активности стоматогнатической системы у больных с дисфункцией жевательных мышц в зависимости от фазы заболевания и клинического варианта. Выделение на основе математико-статистического анализа различных паттернов нарушений жевательной мускулатуры по локальным, региональным, системным клинико-физиологическим показателям и возможного лечебного воздействия окклюзионных сплнтов на восстановление функциональности стоматогнатической системы. Изучение особенностей генерализованных расстройств в рамках клинических подтипов дисфункции жевательных мышц. Изучение жевательной функции на основе субъективных и объективных показателей при различных клинических подтипах дисфункции жевательных мышц. Разработка интегральных показателей для оценки болевых проявлений в стоматогнатической системе у больных с дисфункцией жевательных мышц.

Научная новизна и оригинальность. Впервые выделены показатели активности стоматогнатической системы, статистически значимо связанные с клиническим вариантом дисфункции жевательных мышц, фазой заболевания и показатели общими для обоих критериев. Впервые на основе математико-статистического анализа выделены клинические проявления, которые дифференцируют больных с дисфункцией жевательных мышц на 2 различных паттерна (региональный, регионально-генерализованный) в зависимости от протяженности и выраженности нарушений. Структура и выраженность количественных и качественных показателей дисфункции жевательных мышц зависят от явления фибромиалгизности. Оценка жевательной функции требует одновременной оценки объективных и субъективных показателей, которые описывают различные аспекты жевательной функции у пациентов с дисфункцией жевательных мышц. Впервые показано, что сенсорная гиперчувствительность является информативным критерием, характерным для клинических подтипов дисфункции жевательных мышц. Впервые предложен метод болевой картирования жевательных мышц с оценкой показателя относительной неоднородности болевой карты, что является новым и информативным подход к дисфункциям жевательных мышц. Впервые показано, что моделирование стрессовой нагрузки позволяет выделить изменение болевой толерантности и резистентности жевательной мышцы, существенно не меняющееся в условиях относительного комфорта у пациентов с дисфункцией жевательных мышц, что выявляет некоторые особенности связь стресса и его проявления в локализации боли.

Практическая важность: Структура клинической картины и выраженность клинико-физиологических показателей дисфункции жевательных мышц зависят от клинического варианта, фазы заболевания и наличия генерализации симптомов. Дифференциальная оценка жевательной функции может быть достигнута по субъективным и объективным показателям при применении теста оценки жевательной способности к перемешиванию у пациентов с дисфункцией жевательных мышц. Персонализация диагностики дисфункций жевательных мышц в зависимости от фазы заболевания, клинического варианта может производиться на основании показателей сенсорной гиперчувствительности. Определена диагностическая ценность экспериментального моделирования стрессовой нагрузки и его влияния на количественно-сенсорные показатели у больных с дисфункцией жевательных мышц. Впервые разработана технология локо-регионального исследования боли путем анализа неоднородности пространственного распределения болевой механической чувствительности жевательной мышцы.

Внедрение научных результатов. Результаты научных исследований были внедрены в исследовательский процесс, методологическую и клиническую деятельность в стоматологической клинике Fala Dental, Megalux Dent, в муниципальном стоматологическом центре, в дидактическом учебном процессе на кафедре терапевтической стоматологии ГУМФ «Николае Тестемицану».

ANNOTATION
Bordeniuc Gheorghe
„Clinical-physiological indices in the masticatory muscle dysfunction”
Doctoral thesis in medical sciences, Chişinău, 2023

Thesis structure. The text of the thesis is presented on 120 pages of basic text, processed on the computer, consisting of: list of abbreviations, introduction, 5 chapters, general conclusions, practical recommendations, bibliography from 288 sources and 4 appendices. The illustrative material includes 23 tables, 15 figures and 7 formulas. **Keywords:** temporomandibular disorders, masticatory muscle dysfunctions, clinical-physiological indices, diagnosis.

Field of study: 323.01 – Stomatology.

The purpose of the work: Studying the particularities of masticatory muscle dysfunctions (clinical variant, disease phase) based on the enhancement of the DC/TMD protocol with local, regional and systemic clinical-physiological indices.

Research objectives: Study of the activity of the stomatognathic system in patients with dysfunctions of the masticatory muscles according to the phase of the disease and the clinical variant. Highlighting, based on the mathematical-statistical analysis, of the distinct clinical patterns of masticatory muscle disorders based on local, regional, systemic clinical-physiological indices and the potential therapeutic impact of occlusal splints in rehabilitating the functionality of the stomatognathic system. Studying the peculiarities of generalized disorders within the clinical subtypes of masticatory muscle dysfunction. Study of masticatory performance based on subjective and objective indices in different clinical subtypes of masticatory muscle dysfunction. Development of integral parameters for the assessment of pain manifestations in the stomatognathic system in patients with dysfunctions of the masticatory muscles.

Scientific novelty and originality: For the first time, indices of the activity of the stomatognathic system were highlighted, that are statistically significantly associated with the clinical variant of masticatory muscle dysfunction, the phase of the disease and common indices for both criteria. For the first time, based on the mathematical-statistical analysis, the clinical manifestations were identified, which can differentiate patients with masticatory muscle dysfunctions into 2 distinct clinical patterns (regional, regional-generalized) based on the extent and severity of the disorders. The structure and severity of quantitative and qualitative indices of masticatory muscle dysfunctions are dependent on the phenomenon of fibromyalgias. The assessment of masticatory function requires the simultaneous evaluation of objective and subjective indices, which describe different aspects of masticatory performance in patients with masticatory muscle dysfunction. For the first time, sensory hypersensitivity has been shown to be an informative criterion, characteristic of clinical subtypes of masticatory muscle dysfunction. For the first time, a masseter muscle pain mapping method was proposed with the assessment of the relative heterogeneity index of the pain map. For the first time, it has been shown that operational stress modeling allows highlighting the change in pain tolerance and resistance of the masseter muscle, which does not change essentially in relative comfort conditions in patients with masticatory muscle dysfunctions.

Practical importance: The clinical structure and expression of masticatory muscle dysfunction depends on the clinical variant, the disease phase and the generalization of symptoms. Differentiated assessment of the masticatory function can be achieved by applying subjective and objective indices of the mixing ability assessment test in patients with masticatory muscle dysfunctions. Personalization of the diagnosis of masticatory muscle dysfunctions depending be made based on the indices of sensory hypersensitivity. The diagnostic value of experimental modeling of operational stress and its impact on quantitative-sensory indices in patients with masticatory muscle dysfunctions was determined. For the first time, a loco-regional pain examination technology was developed, by analyzing the heterogeneity of the spatial distribution of mechanical pain sensitivity of the masseter muscle.

Implementation of scientific results. The results of scientific research were implemented in the research process, methodological and clinical activity at the Fala Dental Clinic, Megalux Dent Clinic, IM Municipal Dental Center, in the didactic training process at the Department of Therapeutic Dentistry of USMF "Nicolae Testemiţanu"

LIST OF ABBREVIATIONS

AUC	Area under curve;
CPI	Characteristic Pain intensity;
CS	Central sensitization;
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders;
Di	Dysfunctional Index (Helkimo);
EMG	Electromiography;
ICD-10	International Classification of Diseases (10th revision);
JFLS	Jaw Functional Limitation Scale;
kgf	Kilogram-force;
MMD	Masticatory muscle disorders;
MMI	Mandibular Mobility Index;
MTS	Mean tactile sensitivity;
PPE	Pressure pain endurance;
PPT	Pressure pain threshold;
PTT	Pressure pain tolerance;
RDC/TMD	Research and Diagnostic Criteria for Temporomandibular Disorders;
ROC	Receiver operating curve;
ROM	Range of motion;
SAS	Subjective Assessment Scale;
SHS	Sensory Hypersensitivity Scale;
SSS	Symptom Severity Scale;
TMD	Temporomandibular disorder;
TMI	Temporomandibular Index;
TMJ	Temporomandibular joint;
TOI	Temporomandibular Opening Index;
VAS	Visual Analogue Scale;
WPI	Widespread Pain Index.

BORDENIUC Gheorghe

CLINICAL-PHYSIOLOGICAL INDICES IN THE MASTICATORY
MUSCLE DYSFUNCTION

323.01 – STOMATOLOGY

Summary of Doctor of Medical Sciences Thesis

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