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Muscle Pain Sensitivity and Prevalence of Temporomandibular Disorders in Patients with Narcolepsy with Cataplexy: A Controlled Cohort Study

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Abstract: Disturbed nocturnal sleep contributes to the central sensitization of pain, thus predisposing to orofacial pain. Central disorders of hypersomnolence are characterized by excessive daytime sleepiness (EDS) not linked to impairment of nocturnal sleep or misaligned circadian rhythms. The main disorder of this group is narcolepsy type 1 (NT1), which seems to be related to alterations in pain perception mediation, supposedly caused by low orexin levels. The aim of this study was to evaluate the pain sensitivity and the prevalence of temporomandibular disorders (TMDs) in patients with NT1. After a 3-day hospital evaluation with laboratory polysomnography, 39 consecutive adult patients diagnosed with NT1 and 39 matched heathy controls were evaluated by means of Axis I and Axis II of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) protocol. Furthermore, pain sensitivity was investigated by measuring the pressure pain thresholds (PPTs) on the head–neck muscles by means of a Fischer algometer. No significant differences were found between the PPTs of the two groups for all the muscles evaluated, nor in the prevalence of TMD diagnoses, but the NT1 group reported significantly higher values in the Patient Health Questionnaire (PHQ-9), corresponding to a depressive state. The present study presents an important investigation into NT1 patients, showing no alterations in pain perception and no differences in the prevalence of TMD diagnosis compared to the controls.

Keywords: orofacial pain; narcolepsy; temporomandibular disorders; sleep disorders; pressure pain thresholds; polysomnography; algometer

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1. Introduction

Chronic pain and sleep are linked by a complex bidirectional interplay. Although the underlying neuronal networks and mechanisms are not fully elucidated, a major role seems to be played by the periaqueductal gray, which modulates nociception and sleep stages [1], and by proinflammatory cytokines (e.g., interleukin-6) found at higher concentrations in some pain conditions but also during periods of sleep deprivation [2,3].

Sleep disorders such as insomnia contribute to the increase in perceived pain by preventing adequate psychological and physiological rest [4,5]. On the other hand, pain itself can intrude during sleep causing microarousals and can disturb sleep initiation and maintenance [4,5]. Consequently, there is evidence that disturbed nocturnal sleep increases the risk of pain occurrence and worsens the prognosis in cases of chronic pain by modulating circadian fluctuations of pain [4,6]. Moreover, it should be considered that

chronic pain and disturbed nocturnal sleep contribute to obesity, type 2 diabetes, and depression [4,7].

Orofacial pain caused by temporomandibular disorders (TMDs) [8] is the second most common musculoskeletal disease, causing pain and disability [9,10]. TMD is an umbrella term indicating disorders affecting the temporomandibular joint (TMJ), the masticatory muscles, or both [8]. There is evidence that poor sleep quality is a risk factor for orofacial pain [10], and it is also commonly reported by patients with chronic orofacial pain [11–13]. A higher prevalence of sleep disorders and a relationship between several sleep disorders (insomnia, restless legs syndrome, and obstructive sleep apnea syndrome) and a decrease in pain thresholds were found in a population of TMD patients [14–19]. Therefore, disturbed nocturnal sleep can contribute to the central sensitization of pain, a common phenomenon in chronic TMD patients [14].

Central disorders of hypersomnolence represent a group of disorders characterized by excessive daytime sleepiness (EDS) not linked to the impairment of nocturnal sleep or misaligned circadian rhythms. The main disorder of this group is narcolepsy type 1 (NT1) with a prevalence of 0.02% [20,21]. Narcolepsy is a chronic sleep disorder predominantly characterized by EDS with repetitive sleep attacks, both during inactivity and at work, at school, and even while driving, making this condition socially disabling. These sleep episodes are irresistible, short lasting, caused by a deficiency in hypothalamic hypocretin-1/orexin-1 (<110 pg/mL) [22,23], often associated with dreaming, for a premature occurrence of rapid eye movement (REM) sleep [24,25]. The pathognomonic symptom of NT1 is cataplexy, characterized by a sudden and involuntary loss of muscle tone while awake [26]. Positive strong emotions generally trigger a cataplectic attack, which can last a few seconds to a few minutes with a variable frequency [26]. Sleep paralysis and hypnagogic hallucinations are described but are not specific to NT1 [27]. Non-sleep symptoms have also been described, such as obesity, mood disorders, and headache [28–31]. Despite the little data available on the frequency of pain in NT1 patients, the results encourage further investigation into this correlation because one sample reported not only higher pain occurrence, but also a worse life quality compared to the controls [32]. Additionally, a second sample reported no differences in pain perception with the matched controls [33]. In addition, recent studies have been reported in which hypocretin-1 could have a role in central nociceptive processing [34–36].

An objective assessment of nocturnal sleep and of daytime sleep propensity is required to confirm the clinical diagnosis of NT1 [37]. Laboratory polysomnography (L-PSG) is the reference tool for studying sleep and its influence on physiologic functions. It is essential for the diagnosis of sleep disorders, carrying out a simultaneous registration of electroencephalography (EEG), eye movements by electrooculogram, chin and limbs electromyography (EMG), respiratory air flow, arterial oxygen saturation, and electrocardiogram (ECG) in a laboratory setting with a technician constantly in attendance who is responsible for the correct execution of the study. Moreover, audiovisual recordings are performed during the examination to enhance diagnostic power. Manual scoring of the registrations is performed by experts to define sleep stages and possible events. L-PSG yields the identification of NT1 biomarkers, such as the reduction in sleep latency and in REM sleep latency.

The purpose of this study is to evaluate muscle pain sensitivity and the prevalence of TMDs in patients affected by NT1 compared with healthy controls.

2. Materials and Methods

The present study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement following the checklist [38]. A controlled cohort study was conducted from December 2019 to June 2022 on adult subjects referred to the Center for the Study and Treatment of Sleep Disorders of the Bellaria Hospital in Bologna (Italy), with a suspected case of sleep disorder.

Exclusion criteria included the presence of any medical condition possibly affecting pain (e.g., peripheral neuropathy, fibromyalgia, diabetes, rheumatoid arthritis), the presence of acute or chronic oral conditions (pulpitis, gingival and periodontal disease), and the presence of a pharmacological treatment that could affect pain sensitivity (e.g., analgesics, antidepressants, anxiolytic medications).

All the subjects underwent the following standardized diagnostic procedures to verify their adherence to the selection criteria. A clinical neurological evaluation was performed by an expert in sleep medicine who also administered the Epworth Sleepiness Scale (ESS) [39,40] to assess subjective sleepiness and the Pittsburg Sleep Quality Index (PSQI) [41,42]. As indicated by the American Academy of Sleep Medicine (AASM) [22], L-PSG recordings were carried out for 3 consecutive nights to improve statistical validity. The subjects that were potentially eligible for the study were hospitalized and spent 4 nights in the sleep laboratory. Recordings began the night following patient hospitalization to allow adaptation to the new environment.

PSG was carried out in a dark, soundproofed, and temperature-controlled room and included conventional EEG; EMG of the right and left submental muscles and of the right and left Tibialis muscles; ECG; bilateral electrooculogram; respiratory monitoring; pulse oximetry; and audio/video recordings. The montage of the electrodes was performed following the AASM guidelines and those of the American Association of Sleep Technologists for standard polysomnography [22].

EMG was performed by fixing sensors to the skin in a non-invasive manner. The recordings of submental muscle were used to determine the level of muscle tone, which gradually decreases as one progresses through the deeper stages of sleep, as well as to register bruxism activity. Following the AASM guidelines, one electrode was placed 1 cm lateral and 1 cm above to the right outer canthus, and another electrode was placed 1 cm lateral and 1 cm below the outer left canthus to register electrooculogram. The EMG of the submental muscle was registered by placing one electrode in the midline 1 cm above the inferior edge of the mandible, one electrode 2 cm below the inferior edge of the mandible and 2 cm to the left of the midline, and another one 2 cm below the inferior edge of the mandible and 2 cm to the right of the midline. Monitoring of anterior tibialis muscles was performed by placing the surface electrodes longitudinally and symmetrically in the center of the muscle lengthwise. The electrodes were maintained for the entire duration of hospitalization to collect information about the extension, strength, and duration of muscles activity. Before starting the sleep recording, a calibration test was performed in order to assess baseline values for each parameter (e.g., limb movements, swallowing, maximum voluntary eye movements). The PSG recordings were performed with Brain Quick monitoring (Micromed spa, Mogliano Veneto, TV, Italy) and analyzed using DOMINO Sleep Diagnostic software v.2.2.0 (Somnomedics, Randersacker, Germany). In accordance with AASM guidelines [26], the sleep analyses were performed in 30 s epochs and were directed towards a series of specific parameters: sleep onset latency from lights off; REM sleep latency from the sleep onset; wakefulness after sleep onset; total sleep time (TST); sleep period from sleep onset to lights on; sleep efficiency; percentage of time spent in each sleep stage; awakenings; awakenings per hour; respiratory disturbance index; apnea/hypopnea index; and periodic limb movement index.

Patients of more than 18 years of age who received a diagnosis of NT1 after the L-PSG, according to the ICSD-3 criteria [22], were included and assigned to the N group. Patients with normal neurophysiological results, ruling out nocturnal sleep disorders and excluding EDS, were assigned to the control group.

All subjects were provided with the "Information sheet on participation in the study", signed the privacy policy, and gave written informed consent to be enrolled in the study. The study was approved by the Ethics Committee of the Area Vasta Emilia Centro of the Emilia-Romagna Region (CE-AVEC) with the number 449-2019-OSS-AUSLBO.

All patients were examined by the same operator expert in orofacial pain following the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) [43], which is considered

the gold standard for TMD diagnoses. The protocol includes a clinical examination using reliable and well-operationalized diagnostic criteria (AXIS I) to evaluate physical signs and symptoms, such as TMJ movement disorders, TMJ sounds, TMJ pain on palpation, and masticatory muscle pain on palpation. An evaluation of the psychological status of the subject and pain-related disability (Axis II) was also performed. The patients were asked to fill out the TMD pain screener [44], the Graded Chronic Pain Scale (GCPS) [45] to describe pain intensity and pain-related disability, the Jaw Functional Limitation Scale (JFLS) [46] to evaluate functional status of the masticatory system, the Patient Health Questionnaire-9 (PHQ-9) [47] to assess psychological distress due to depression, the Generalized Anxiety Disorder-7 (GAD-7) assessment [48], the physical symptoms questionnaire (PHQ-15) [49], and the Oral Behaviors Checklist (OBC) [50] to investigate the frequency of oral parafunctional habits. Pain sensitivity was investigated by the measurement of pressure pain thresholds (PPTs) [51], which can be defined as the minimum pressure inducing pain and represent a reliable parameter to investigate pain sensitization [52,53]. The PPTs were evaluated by one calibrated examiner with a Fischer algometer (Pain Diagnostics and Thermography, Great Neck, NY, USA), a force gauge fitted with a rubber disc that had a surface area 1 cm^2, which when pressed against the surface of a person's body, measures pressure in kg/cm^2, with a range of up to 10 kg and 100 gr divisions. The device consists of a metal rod with a male thread on one end, onto which the rubber disc is screwed. Pressure exerted on the rod moves the indicator in a clockwise direction. Pressing the zeroing knob returns the indicator to zero after each measurement; the force value obtained is held until the zeroing knob is pressed, allowing readings even after the algometer is removed from the subject's body.

The examiner trained for one week, learning to reach an increasing pressure rate of 100 gr/sec continuously, as suggested by Fischer [52] and Jensen [54], who demonstrated that a higher pressure-increasing rate may lead to overestimation of PPTs. At the start of the examination, the subjects were familiarized with the measurement procedure and equipment by means of a demonstration on the right forearm and were instructed to keep their teeth slightly apart, in order to avoid contraction of the jaw-closing muscles during stimulation. During the examination, subjects were seated in a standardized position. While the examiner increased the pressure, the sensation at some point involved pain and the subjects were given standardized instructions to signal that the PPT was reached by saying "stop". The pressure at that moment was then read off from the instrument and recorded as the PPT. Subjects were not informed of their PPT values and the operator held the pressure indicator out of sight in order to avoid bias. The muscles examined on both sides of the body were the masseter, anterior, middle, and posterior bellies of the temporal, the ventral portion of the sternocleidomastoid, the occipital, splenius capitis, and the thenar eminence (as a reference far from the head–neck district). All measurements were performed between 7:00 p.m. and 8:00 p.m. The collected data were handled by the author who performed the statistical analysis, who was blinded to which group the subjects belonged to.

Statistical Analysis

Considering differences in PPTs among groups as the primary outcome, the minimum sample size was computed with an effect size of 0.4, α error of 0.05, and β error of 0.20. The results indicate a total minimum sample size of 66 subjects. After testing the PPT values' normality distribution, they were compared between groups by means of t test for independent samples. The comparison of TMD prevalence between groups was computed using the χ^2 test. The results of the DC/TMD Axis II questionnaires were compared between groups using the χ^2 test. Statistical analyses were performed using SPSS software version 25.0 (IBM, Armonk, NY, USA).

3. Results

After the clinical evaluation, 184 subjects were considered potentially eligible. The PSG investigation excluded the following subjects: 46 affected by idiopathic hypersomnia; 15 subjects affected by NT2; 21 that presented comorbidities that could alter nociception; and 20 suffering from other sleep disorders, such as obstructed sleep apnea (OSA), parasomnias, and restless legs syndrome. Forty-three subjects registered normal neurophysiological parameters, showing they were not affected by sleep disorders nor by EDS and were therefore eligible for the control group, but three did not agree to participate in the study. Afterwards, two groups were formed: the N group was composed if 39 subjects diagnosed with NT1 and the control group (C), also composed of 39 heathy individuals. Figure 1 presents the flow diagram of the study.

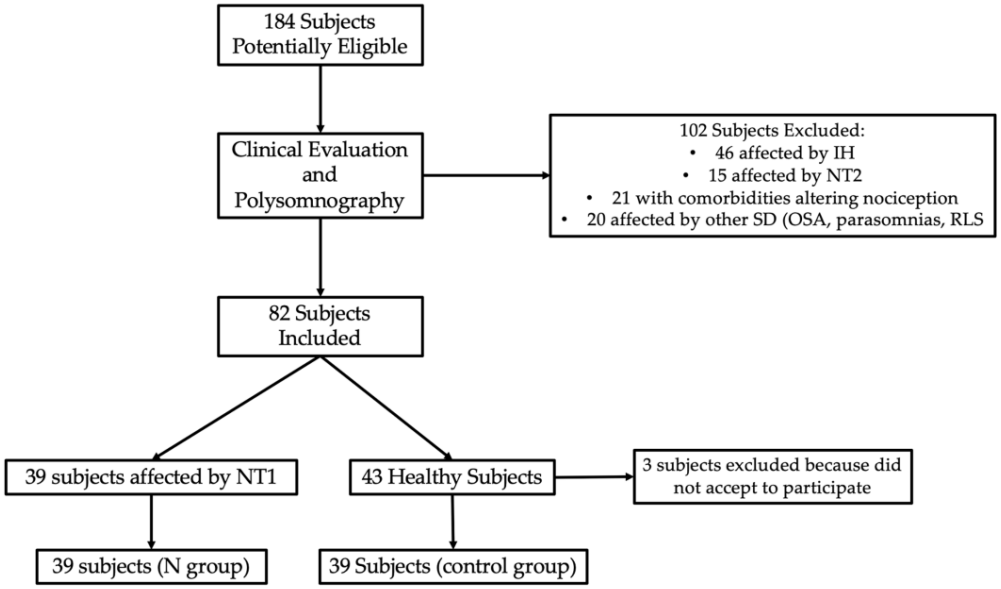

Figure 1. Flow diagram of sample selection. IH = idiopathic hypersomnia; NT2 = narcolepsy type 2; SD = sleep disorder; OSA = obstructed sleep apnea; RLS = restless legs syndrome).

Table 1 reports the sample description; the results of the ESS, PSQI, and TMD pain screener questionnaire; the sleep architecture; and the AHI. As expected, ESS scores were significantly higher in the N group. Sleep onset latency (SL), that is, the time it takes a person to fall asleep after lights off, and rapid eye movement (REM) sleep onset latency (LR), or the time it takes a person to reach the first REM sleep stage after turning the lights off, were significantly lower in the NT1 subjects, while the percentage of total sleep time spent in sleep stage 1 (%TSTN1) was significantly longer as previously reported [55]. The amount of time subject spent awake after initially falling asleep and before they woke for good (WASO) was not significantly different between the N group and C group.

Table 2 reports the PPTs recorded in the study groups. Because no significant differences were found between right and left side PPTs for all muscles, the mean PPT value between the right and left side was computed for each muscle. No significant differences were found between the PPTs of the two groups for all the muscles evaluated.

Table 3 reports the prevalence of TMD diagnoses, reported TMJ noises, reported headache, and muscle pain on palpation in the two groups. No significant differences were found in the prevalence of these parameters between groups.

Table 4 shows the results of the questionnaires of DC/TMD Axis II. PHQ-9 over-cut-off scores were significantly higher in the N group.

Table 1. Sample description, sleep architecture, and AHI.

Variables	Group N (n = 39)	Group C (n = 39)	*p*=
Age (mean ± SD)	38.69 ± 10.89	43.13 ± 12.07	0.092
Gender	16 ♂ (41.0%) 23 ♀ (59.0%)	22 ♂ (56.4%) 17 ♀ (43.6%)	0.174
ESS	14.05 ± 4.80	8.09 ± 5.27	0.001 *
PSQI	7.68 ± 2.57	6.75 ± 4.19	0.267
TMD pain screener over cut-off	10.2% (n = 4)	28.2% (n = 11)	0.021 *
TIB (min)	484.99 ± 66.89	506.79 ± 66.47	0.377
LS (min)	5.15 ± 7.59	20.14 ± 19.27	0.001 *
LR (min)	27.13 ± 37.88	81.90 ± 14.68	0.001 *
TST (min)	413.21 ± 53.21	396.35 ± 63.58	0.406
WASO (min)	66.63 ± 47.20	90.30 ± 77.88	0.254
%TST N1	9.91 ± 6.78	3.23 ± 1.57	0.004 *
%TST N2	39.28 ± 8.07	42.56 ± 9.70	0.297
%TST N3	29.46 ± 12.54	29.88 ± 10.51	0.926
%TST REM	21.35 ± 5.62	24.33 ± 3.05	0.120
AHI	2.21 ± 3.22	0.96 ± 1.76	0.256

p values marked with * show a statistically significant difference between groups. ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index, TMD = temporomandibular disorder; TIB = time in bed; LS = sleep latency; LR = REM latency; TST = total sleep time; WASO = wakefulness after sleep onset; REM = rapid eye movement; AHI = apnea hypopnea index.

Table 2. Mean PPT and standard deviation (SD) recorded in the two groups (kg/cm^2) and comparisons between the groups (*t* test).

Muscles	Group N (n = 39)	Group C (n = 39)	t=	*p*=
Anterior Temporal	2.53 ± 0.80	2.43 ± 0.76	−0.753	0.442
Middle Temporal	2.97 ± 1.04	2.89 ± 1.00	−0.437	0.634
Posterior Temporal	3.35 ± 1.07	3.24 ± 0.99	−0.360	0.500
Masseter	2.07 ± 0.71	1.98 ± 0.63	0.571	0.392
Sternocleidomastoid	1.60 ± 0.59	1.58 ± 0.51	−1.150	0.788
Occipital	2.95 ± 1.23	2.96 ± 1.22	0.364	0.948
Splenius capitis	2.73 ± 1.02	2.18 ± 0.75	−1.831	0.238
Thenar	4.65 ± 1.73	4.51 ± 1.67	0.403	0.606

PPT = Pressure Pain Threshold.

Table 3. Comparison of prevalence of TMD diagnoses between the two groups (X^2 test). Prevalence is reported as percentage and number of subjects.

	Group N (n = 39)	Group C (n = 39)	X^2=	*p*=
TMD	28.2% (n = 11)	38.5% (n = 15)	0.923	0.337
Muscle TMD	20.5% (n = 8)	23.1% (n = 9)	0.075	0.784
Articular TMD	23.1% (n = 9)	28.2% (n = 11)	0.269	0.604
Reported Headache	38.5% (n = 15)	30.8% (n = 12)	0.510	0.475
Pain on muscle palpation	33.3% (n = 13)	33.3% (n = 13)	0.000	1.000

TMD = temporomandibular disorders.

Table 4. Comparison of prevalence of over cut-off scores of the Axis II DC/TMD questionnaires between the two groups (X^2 test).

Questionnaires	Group N (n = 39)	Group C (n = 39)	X^2=	*p*=
GCPS 2.0 Chronic Orofacial Pain	23.1% (n = 9)	28.2% (n = 11)	0.269	0.604
JFLS-20	23.1% (n = 9)	7.7% (n = 3)	4.754	0.093
PHQ-9	74.4% (n = 33)	56.4% (n = 22)	20.844	0.006 *
PHQ-15	69.2% (n = 27)	66.7% (n = 26)	0.059	0.808
GAD-7	56.4% (n = 22)	43.6% (n = 17)	1.282	0.258
OBC	56.4% (n = 22)	52.6% (n = 20)	1.040	0.594

GCPS = Graded Chronic Pain Scale; JFLS-20 = Jaw Functional Limitation Scale; PHQ-9 = Patient Health Questionnaire-9; PHQ-15 = Patient Health Questionnaire-15; GAD-7 = Generalized Anxiety Disorder-7; OBC = Oral Behavior Checklist. * = significant difference between the groups.

4. Discussion

The present investigation is one of the first to evaluate the pressure pain threshold (muscle pressure pain sensitivity) of the masticatory muscles and the prevalence of TMD in a group of patients affected by NT1 compared to healthy controls. The groups proved to be homogeneous for age and gender with the expected differences in sleep architecture.

The main outcome of this study is represented by the absence of significant differences in the PPTs between the two groups for all the muscles evaluated (Table 2). It is important to underline that no differences were found even in the PPTs of the thenar muscle, which does not belong to the area of the head and neck muscles, thus indicating the absence of central pain sensitization in the sample recruited. No differences emerged for the prevalence of TMD between the two groups either.

Dauvilliers and coworkers in 2011 investigated chronic pain in patients affected by narcolepsy with cataplexy (NT1) by means of questionnaires and interviews [32]. Subjective pain assessment showed more frequent pain complaints in NT1 patients compared to the controls, a finding unrelated to medication use and significantly related to lower quality of life and depression [32]. The outcomes do not allow a symptomatic cause of pain in NT1 to be formally ruled out, but it is important to consider that depressive symptoms and sleep quantity emerged as significant determinants of the presence of pain. In 2015, Spielberger evaluated the pain perception in 13 people with NT1 and matched healthy controls using standardized quantitative sensory testing [33], that consists of the assessment of the mechanical detection threshold, vibration detection threshold, warm detection threshold, cold detection threshold, cold pain threshold, heat pain threshold, mechanical pain threshold, and PPT. None of the parameters regarding perception of sensory or painful stimuli differed significantly between the groups, and the authors indicated that the increased pain referred by NT1 patients does not result from an altered perception of sensory or nociceptive stimuli. The outcomes of this study support the presence of a psychological component in NT1 patients' pain reporting. In fact, the N group showed a significant difference in PHQ-9 score, a questionnaire evaluating the depressive state of the subject, indicating a higher prevalence of depressive symptoms in NT1 patients ($p = 0.006$), which has already been described in studies with a larger sample size [28,56]. However, the absence of significant differences in the PPTs of head and neck muscles between the two groups does not meet the assumption of a possible modification in NT1 patients' pain thresholds formulated by Dauvillers. These results sustain the findings of Spielberger and coworkers, with a larger sample size, and support the hypothesis that hypocretin-1 deficiency in NT1 subjects does not lead to dysregulation in the nociception and that EDS does not impair to such an extent that modifies pain perception, although some studies speculate that pain sensitivity is altered in sleepy individuals [57,58].

Concerning the prevalence of TMD, previous studies described an increased frequency of migraine and tension-type headache [30,31,59]. No significant differences emerged

between the NT1 patients and controls in the present investigation, and the N group reported suffering from headaches similarly to the controls, in accordance with the findings by Dauvilliers and coworkers [32].

The analysis of the over cut-off scores of DC/TMD Axis II did not show significant differences among groups in all questionnaires administered, except the PHQ-9, an instrument for screening, diagnosing, monitoring, and measuring the severity of depression. This is a very interesting outcome, adding value to the study, as it is in agreement with data reported in the literature. In particular, patients with NT1 showed a greater prevalence of depression with mild and moderate symptoms compared to healthy controls [60]. According to some authors, the orexinergic system could be involved in the pathophysiology of psychiatric disorders [61]. It has been suggested that orexin-1 deficiency could prevent appropriate management of emotions and it could therefore be related to depressive symptoms [62]. It is still unclear if the presence of these alterations belongs to the pathophysiology of narcolepsy or if it is secondary to its manifestation, but what is certain is the importance of monitoring the patients affected by narcolepsy for the presence of depression. The JFLS is a questionnaire that evaluates the limitations of mandibular function and, even if not significantly ($p = 0.093$), the N group showed a trend in higher scores than the controls; 23.1% of NT1 patients had scores over cut-off, versus 7.7% of the control group. These data suggest plausible susceptibility to TMD dysfunction and discomfort in N patients.

The outcomes of the present study should be interpreted in light of some limitations. Despite the fact that all the questionnaires administered were validated and internationally recognized as the gold standard for TMD diagnosis, the absence of a complete psychiatric evaluation, which would have provided more reliable descriptions of the whole spectrum of mental disorders, limits the validity of the conclusions. Furthermore, not having assessed the presence of bruxism represents a bias: despite the association between sleep bruxism and TMD, it is still a matter of debate [63]. There is growing evidence on the possible correlations between awake bruxism and orofacial pain [64]. Therefore, the presence of bruxism in the population of the present study represents a possible confounder.

The non-significant differences in the PPTs of the muscles evaluated and in the prevalence of TMD in the N group, despite the high prevalence of depressive symptoms, suggest the presence of pain in these patients should be carefully considered because it seems to have a multifactorial etiology. To this end, the personal characteristics of a single patient could correspond to manifold clinical presentations. Despite having not found significant differences between the two groups, the results are of remarkable interest and should be taken into consideration in both clinical and research settings to avoid publication bias.

In the present study, the narcolepsy group included only NT1, characterized by low levels of hypocretin-1, thus permitting us to evaluate the impact of hypocretin deficiency, together with REM sleep propensity and EDS. Even if hypocretin-1 has been reported to have antinociceptive effects [34–36], the results of the present study showed no differences in muscle pain sensitivity between NT1 patients and healthy controls, in accordance with the results of a previous study [33] but with a larger sample size.

5. Conclusions

The present study investigated the muscle sensitivity (PPT) and the prevalence of TMD in NT1 patients. Assessments were performed by means of objective measurements, viz., the Fischer's algometer and the gold standard DC/TMD protocol, together with validated questionnaires. The outcomes show that painful pressure stimuli perception was not altered in the muscles evaluated, indicating that muscle pain sensitivity was similar between the NT1 patients and healthy controls. Furthermore, no differences in the prevalence of TMD diagnoses and of headache emerged from the present data between the two groups. The present results encourage further research on the correlation between pain and NT1, underlining the importance of the bio-psycho-social sphere Future investigations could involve a specific psychiatric evaluation to verify possible interplay between orofacial pain and depression, as well as other mental health conditions in NT1 subjects. Thereafter,

studies of basic research could be conducted to explain the molecular or genetic features causing such alterations.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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