

Article

Craniomandibular Disorders in Pregnant Women: An Epidemiological Survey

Grazia Fichera ¹, Alessandro Polizzi ^{1,*} , Simone Scapellato ^{1,2} , Giuseppe Palazzo ¹ and Francesco Indelicato ¹

¹ Department of General Surgery and Surgical-Medical Specialties, University of Catania, 95124 Catania, Italy; graziafichera@hotmail.it (G.F.); simonescapellato@hotmail.com (S.S.); gpalazzo@unict.it (G.P.); indelicato@policlinico.unict.it (F.I.)

² Department of Biomedical, Odontostomatological Sciences and of Morphological and Functional Images, University of Messina, 98125 Messina, Italy

* Correspondence: alexpoli345@gmail.com

Received: 6 April 2020; Accepted: 1 June 2020; Published: 4 June 2020



Abstract: Temporomandibular joint (TMJ) disorder has been reported to be 1.5 to two times more common in women than men. Such a gender-based difference could be attributed to behavioral, hormonal, anatomical, and psychological characteristics. Physiological hormonal differences between genders could be one of the possible explanations for the higher incidence of temporomandibular disorder (TMD) in women. As the plasma level of certain female hormones increases during gestation, it could be assumed that there is a higher prevalence of dysfunctional signs and symptoms in pregnant women. We performed an epidemiological survey based on screening for TMD in a group of 108 pregnant women and found that 72% of young women reported significant signs of TMJ disorders, 9% of the young women reported mild signs of TMJ disorders, and 19% of the included subjects reported no signs or symptoms of TMD. The presence of estrogen receptors in the temporomandibular joint of female baboons could be the basis of an explanation for the increased prevalence of dysfunction in young women reported in the literature and the high feedback we have seen of joint noises in pregnant women. On the basis of the present findings, it could be assumed that gestation period could represent a risk factor for craniomandibular dysfunctions.

Keywords: temporomandibular joint; pregnancy; temporomandibular disorder; growth; clinical trial

1. Introduction

Dysfunction of the masticatory system, including the temporomandibular joint (TMJ), muscular and dental system, and the supporting bones, is called temporomandibular disorder (TMD) [1].

Adults are more affected by TMD as compared with children in a range of between 40% and 70%, however, a relevant high incidence of TMD has been found among subjects in mixed dental dentition [1–3]. Ethnicity, age, geographical location, and time of assessment influence the prevalence, causes, and factors that affect TMD, as well as the signs and clinical symptoms [4–7]. According to previous findings, TMD is generally reported to be 1.5 to two times more common in women as compared with men, and this difference is attributed to behavioral, hormonal, anatomical, and psychological factors [8,9]. In general, women are more affected than men by craniomandibular dysfunctions with a ratio of 4 to 1 [10–14]. The prevalence of clicks, headaches, teeth tightening, hypomobility, difficulty in chewing, and neuromuscular symptoms has been shown to be significantly higher among young women (<30 years) [15–20]. Moreover, there was a significant correlation between the severity of symptoms and age among women, and a relative reduction in clinical symptoms with age in

both sexes [10–13,15,16,21,22]. Previous evidence reported that estrogen receptors are localized in the TMJ tissues, such as chondroid tissue of condyle and retrodiscal tissues [6,17,18,23–27]. In this respect, the hormone, estrogen, could influence the incidence of TMD, and its levels can affect the development, restitution, and metabolism of the temporomandibular joint, bone, and associated structures [7,23,25,28–34]. Estrogen can be related to TMD by regulating the pain mechanisms in the expressions of TMD [35]. For example, receptors for estrogens were found in both the peripheral and central nervous systems which would suggest that estrogens are capable of modifying pain signaling [36]. Moreover, estrogen receptors (ER α , ER β) were also reported in the dorsal root ganglion (DRG) and in the trigeminal nerve nucleus. Estrogen can act as a pro- and anti-nociceptive, depending on the pain signaling type. In physiological pain, estrogen decreases pain, whereas, in inflammatory pain, the effect of estrogen depends on the inflammation type. In acute inflammatory pain, estrogen has an anti-nociceptive effect. On the contrary, in chronic inflammatory pain, this hormone has been documented to have a pro-nociceptive effect due to the presence of its receptors in tissues of both the peripheral and central nervous systems [36–39].

Thus, physiological hormonal differences between males and females could be one of the possible explanations for the higher incidence of TMD in the female. Given that the plasma level of some female hormones increases during gestation, it could be postulated that there is a higher prevalence of dysfunctional signs and symptoms in pregnant women than the frequencies reported in the literature for the same sex. In this respect, the aim of the present study was to assess the presence of TMJ disorders in a cohort of pregnant women.

2. Materials and Methods

2.1. Study Design

This study followed the Helsinki Declaration on medical protocols and ethics and received positive response by the Approval Board of the School of Dentistry, University of Catania (protocol no. 14/19). The study sample included subjects followed at a private practice specialized in gynecology and gynecologic radiology, in Catania (Italy), between January 2016 and March 2020. For the investigation, subjects were recruited base on the following inclusion criteria: subjects at the sixth month of pregnancy, aged between 19 and 35 years, and absence of severe dental pathology potentially affecting the perception of TMD and craniofacial dysmorphism. The anamnestic data were collected using yes-no questionnaires in compliance with the Helkimo anamnestic dysfunction index (Ai) (Figure 1) and subjects were classified as Ai 0 (no symptoms), I (mild symptoms), and II (severe symptoms) based on the information obtained.

Screening for craniomandibular dysfunctions was done by following the Helkimo dysfunction index guidelines (Figure 2) [40–42].

All examinations were performed by the same expert, blinded gnathologist. In particular, clinical examination of masticatory apparatus was performed using the Helkimo clinical dysfunction index (Di), which is based on five domains each evaluating one of the following signs of TMJ dysfunction: limited TMJ mobility, limited TMJ function, jaw muscle pain to palpation, TMJ pain to palpation, and pain during mandibular movement. Jaw movements were evaluated in order to highlight the presence of any limitations. The temporomandibular joint was examined for the diagnosis of joint noise, taking into account possible deviations and deflections of the lower median line over three chewing cycles. Palpation of the chewing muscles and the temporomandibular joint was carried out, and the mandible excursions were examined to assess the presence of pain. Scores for each of the domains were based on the three-level scale of severity, i.e., 0 (no symptoms), 1 (mild symptoms), and 5 (acute symptoms) and were summed up to obtain a total dysfunction score ranging from 0 to 25 points, with a high score indicating a higher temporomandibular dysfunction. In order to obtain comparative assessment, data of the study group were matched with a control sample of female subjects living in the same geographic area who had been referred to the same gynecology clinic for routine controls.

The recruitment of the control group was based on the same inclusion criteria as the study group except for the pregnancy status.

DYSFUNCTIONAL ANAMNESTIC QUESTIONNAIRE	
Name.....	Surname.....
Date of birth.....	AGE.....
Profession.....	
HAVE YOU EVER EXPERIENCED ANY OF THE FOLLOWING SYMPTOMS (please mark with an x the affected boxes)	
<input type="radio"/> PAIN TO THE FACE AND/OR TO MASCELLARS	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> PAIN DURING JAW MOVEMENTS (OPENING/CLOSING AND CHEWING)	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> DIFFICULTY OPENING WIDELY OR BITING ON A HUGE BOLO	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> SENSE OF FATIGUE IN THE FACE AND JAWS	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> DIFFICULTY CHEWING	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> LOCKING THE JAW (UNABLE TO OPEN AND CLOSE THE MOUTH)	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> JOINT NOISES	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>
<input type="radio"/> TEETH LOCKING	never <input type="checkbox"/> often <input type="checkbox"/> frequently <input type="checkbox"/> always <input type="checkbox"/>

Figure 1. Example of the anamnestic Helkimo index.

HELKIMO DYSFUNCTIONAL CLINICAL INDEX (1974)		
A	Symptom: Limiting movement	
	Criterion: No limitation	0
	Modest limitation	1
	Severe Limitation	5
B	Symptom: Limitation of ATM functionality	
	Criterion: Regular movements without joint noise and detour to Open or Close <2mm	0
	Joint noises in one or both joints and/or deviation > 2mm opening or closing	1
	Locking and/or dislocation of ATM	5
C	Symptom: Muscle pain	
	Criterion : No palpation pain	0
	Pain in 1-3 sites palpated	1
	Pain in 4 or more palpated sites	5
D	Symptom: PAIN at ATM	
	Criterion: No palpation pain	0
	Pain at side palpation	1
	Pain at the rear palpation	5
E	Symptom: Pain during jaw movements	
	Criterion: No pain	0
	Pain during a movement.	1
	Pain during two or more movements	5
F	Sum of A-B-C-D-E - Score for Malfunctions (0-25)	

Figure 2. Example of the Helkimo clinical dysfunction index questionnaire filled out by one included patient.

2.2. Power Sample Analysis

A preliminary evaluation of sample size power was performed on 20 subjects (10 in the study group and 10 in the control group), the analysis suggested that 79 patients for each group were required to reach the 80% power to detect a mean difference of 7.2% [43] of incidence of clinically assessed joint click between study and control groups, with a confidence level of 95% and a beta error level of 20%.

However, according to the inclusion criteria, it included 108 subjects in the study group and 90 subjects in the control group which increased the robustness of the data.

2.3. Statistical Analysis

The Kolmogorov–Smirnov test was preliminarily performed to test the normality of the data. Since the data showed homogeneous variance, parametric tests were used to evaluate and compare measurements.

For those subjects reporting positive values from the anamnestic index, data obtained from the dysfunction index were recorded on a specific spreadsheet. Datasets were analyzed using SPSS® version 24 Statistics software (IBM Corporation, 1 New Orchard Road, Armonk, New York, USA). The incidence of TMD was detected as percentage values within the sample size. Chi-square test coefficient was used to compare the distribution data obtained from the anamnestic and dysfunction forms between each group. The level of significance was set at $p < 0.05$.

3. Results

One hundred and eight pregnant females (mean age 27.4 ± 3.8) were finally recruited to participate in the survey of the present investigation and 72% of young women reported significant signs of TMJ disorders. Thus, they were allocated to belong to the DII group (moderate dysfunctional) according to the anamnestic Helkimo index; 9% of young women reported slight signs of TMJ disorders and were allocated to the DI group (slightly dysfunctional). Consequently, 19% of the included subjects did not report signs or symptoms of TMD and were allocated to the the D0 group.

Ninety female subjects were enrolled in the control group (mean age 26.2 ± 4.5) and 41% of young women reported significant signs of TMJ disorders. Thus, they were allocated to the DII group (moderate dysfunctional) according to the anamnestic Helkimo index; 11% of young women reported slight signs of TMJ disorders and were allocated to the DI group (slightly dysfunctional). Consequently, 48% of the included subjects did not report signs or symptoms of TMD and were allocated to the D0 group.

Table 1 shows the distribution of data obtained with the anamnestic Helkimo index and assessed using the Chi-square test ($p < 0.05$). Table 2 shows the distribution of data obtained with the Helkimo dysfunction index and assessed using the Chi-square test. In both groups, all subjects in the DII group reported TMJ click, whereas subjects in the DI group reported muscular pain ($p < 0.05$).

Table 1. Data distribution from the anamnestic form (Helkimo’s index). Significance set at $p < 0.05$ according to the Chi-Square test.

		TMJ Dysfunction			
		Positive	Negative	Total	
Study Group	Observed	87	21	108	$p < 0.05$
	Percentage (%)	81	19	100	
Study Group	Observed	47	43	90	
	Percentage (%)	52	48	100	

Table 2. Data distribution from the anamnestic form (Helkimo’s index). Significance set at $p < 0.05$ according to the Chi-Square test.

		Articular Signs	Muscular Pain	Total	
Study Group	Observed	87	0	87	
	Percentage (%)	100	0	100	
Study Group	Observed	37	10	47	
	Percentage (%)	79	21	100	

4. Discussion

From the literature review, it can be seen that the incidence of craniomandibular dysfunctions, except for a few exceptions, shows no gender differences in school-age patients, whereas, for adults, prevalence of signs is observed dysfunctional in the female sex. It can be hypothesized with great certainty that, after adolescence, physiological, psychological, and morphological differences are taking over. With regard to physiological differences, in addition to the effects of hormonal regulation of metabolic activities, women are much more susceptible to pulp stimulation pain. Men tolerate deep pain much more readily than women, and pain tolerance in general and the threshold of skin pain are lower in women than in men [44–46].

Patients with craniomandibular dysfunction, and especially women, similar to periodontitis [28,47–53] have a lower pain tolerance than the control group [42,54], and a lower pain threshold [55,56]. In addition, emotional stress increases pain by accelerating activities in the neural system, which is, in turn, stimulated by harmful impulses. Anxiety, depression, anger, induce autonomous, visceral and skeletal activities, and the interactions between these biological systems are illustrated in the pain-anxiety-tension cycle proposed by some authors to explain some forms of acute pain, and often observed in pathologies affecting the skeletal-muscular system [57–61].

Pain causes anxiety, which induces both prolonged muscle spasms at pain sites and trigger points, as well as vasoconstriction, ischemia, and release of pain-mediating substances. Similarly, depression has a profound effect on peripheral symptoms, interacting through the thalamus and hypothalamus. Catecolo-methyltransferases (COMT) is an important enzyme that inactivates neurotransmitters and regulators of the central and peripheral nervous system. Patients with craniomandibular dysfunction have a low erythrocyte level of COMT as compared with control subjects, and therefore appear to be predisposed to depression. With a few exceptions, women suffer much more than men from depression and this psychophysiological difference could explain the results of his studies [62].

Depression is easier to match among young women and usually decreases with age; however, symptoms of depression are less common among young males [24]. This could justify the significant correlation between the severity of symptoms and age for women, and the decrease in the number of symptoms for both sexes previously found [21,63,64]. The authors also saw that young women have a high incidence of clicks, headaches, teeth tightening, hypomobility, difficulty in chewing, and neuromuscular symptoms. This could be explained by the fact that women are much more susceptible to tissue alterations and, in particular, to those of the condyle-disc complex [24,64].

The teeth tightening found in young women would represent a functional expression of specificity of response originating from the activity of large muscles and high residual muscle tension. Chronic muscle hyperactivity with the maintenance of high residual muscle tension could initiate numerous pathophysiological mechanisms [49,65–67].

It must also be said that women from puberty to menopause have a hormonal structure that varies cyclically in a physiological way. During pregnancy, this situation changes further, as, after fertilization, the lute body remains active, magnifying large amounts of estrogen and progesterone. After the third month, it is no longer essential for the continuation of pregnancy, as its endocrine function changes to the placenta, so it regresses. The placenta, as well as an organ responsible for the exchanges between the fetus and the mother, is also an endocrine organ, which separates at least four types of hormones, i.e., a gonadotropin, estrogen, progesterone, and relaxin [67]. The effects of sex hormones in target tissues are varied and very significant. They stimulate collagen and protein synthesis, increased vasal reactivity, alteration of endothelial permeability, and prostaglandins synthesis [67–70]. They also have an effect on the immune system, having a role in antibody formation and in stem cell differentiation and proliferation. They inhibit leucocyte proliferation in rats and, in humans, suppress the transformation of lymphocytes. Estrogens also tend to increase the immune response, as opposed to androgens [71].

The presence of estrogen receptors in the temporomandibular joint of female baboons [16,71] could be the basis of an explanation for the higher prevalence of the dysfunction in young women reported in the literature [72–83], and the high feedback we have noted of joint noises in pregnant women.

Relaxin, which is mainly found in serum and mammalian tissues, especially during pregnancy, has a series of actions that together promote gestation and prepare the female reproductive apparatus for childbirth. The connective tissue of pubic symphyses causes the transformation from cartilage to the more fluid and flexible with ligament formation between the two pubic bones. They increase collagen texture and extensibility [83–85] and dilate and makes the cervix softer.

On the basis of previous evidence confirming the prevalence of TMD in female [24,26,72], our findings would suggest that pregnancy can be more susceptible from TMD and that gestation is a predisposing factor for craniomandibular dysfunctions [58–63].

The hypothesis that relaxin, reaching high levels during pregnancy, affects the tenderness of joint tissues, including the TMJ [74,75], could explain the high incidence of clicks in the pregnant young women found in the present study. Further studies, based on this assumption, are warmly required in order to provide new information on the potential effects of hormone levels on the development of TMD.

The limitation of this study is the absence of a quantitative distinction between physical assessment and psychological assessment of TMD and further studies should include this comparative evaluation in the methodology.

5. Conclusions

Female subjects in pregnancy status could be more susceptible to TMD due to a physiological increment of estrogenic hormones levels. However, further studies are needed to better understand the role of TMD during pregnancy.

Author Contributions: G.F. has drafted the work and performed segmentations; A.P. and S.S. has performed the experimental procedures; G.P. and F.I. has validated the results. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

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

References

1. Furquim, B.D.; Flamengui, L.M.; Conti, P.C. TMD and chronic pain: A current view. *Dent. Press J. Orthod.* **2015**, *20*, 127–133. [[CrossRef](#)] [[PubMed](#)]
2. Castelo, P.M.; Gaviao, M.B.; Pereira, L.J.; Bonjardim, L.R. Relationship between oral parafunctional/nutritive sucking habits and temporomandibular joint dysfunction in primary dentition. *Int. J. Paediatr. Dent.* **2005**, *15*, 29–36. [[CrossRef](#)] [[PubMed](#)]
3. Mackie, A.; Lyons, K. The role of occlusion in temporomandibular disorders—a review of the literature. *N. Z. Dent. J.* **2008**, *104*, 54–59. [[PubMed](#)]
4. Okeson, J.P. *Management of Temporomandibular Disorder and Occlusion -E -Book*; Elsevier Health Sciences: Amsterdam, The Netherlands, 2008; pp. 1–333. [[CrossRef](#)]
5. Chisnoiu, A.M.; Chisnoiu, R.; Moldovan, M.; Lascu, L.M.; Picos, A.M. Etiological factors associated with temporomandibular joint disorder - Study on animal model. *Rom. J. Morphol. Embryol.* **2016**, *57*, 185–189. [[PubMed](#)]
6. Mortazavi, S.H.; Motamedi, M.H.; Navi, F.; Pourshahab, M.; Bayanzadeh, S.M.; Hajmiragha, H.; Isapour, M. Outcomes of management of early temporomandibular joint disorders: How effective is nonsurgical therapy in the long-term? *Natl. J. Maxillofac. Surg.* **2010**, *1*, 108–111.
7. Lo Giudice, A.; Rustico, L.; Caprioglio, A.; Migliorati, M.; Nucera, R. Evaluation of condylar cortical bone thickness in patient groups with different vertical facial dimensions using cone-beam computed tomography. *Odontology* **2020**. [[CrossRef](#)]
8. Lo Giudice, A.; Brewer, I.; Leonardi, R.; Roberts, N.; Bagnato, G. Pain threshold and temporomandibular function in systemic sclerosis: Comparison with psoriatic arthritis. *Clin. Rheumatol.* **2018**, *37*, 1861–1867. [[CrossRef](#)]

9. Ferendiuk, E.; Zajdel, K.; Pihut, M. Incidence of otolaryngological symptoms in patients with temporomandibular joint dysfunctions. *Biomed Res. Int.* **2014**, *2014*, 824684. [[CrossRef](#)]
10. Velly, A.M.; Schiffman, E.L.; Rindal, D.B.; Cunha-Cruz, J.; Gilbert, G.H.; Lehmann, M.; Horowitz, A.; Fricton, J. The feasibility of a clinical trial of pain related to temporomandibular muscle and joint disorders: The results of a survey from the Collaboration on Networked Dental and Oral Research dental practice-based research networks. *J. Am. Dent. Assoc.* **2013**, *144*, e1–e10. [[CrossRef](#)]
11. Leonardi, R.; Loreto, C.; Talic, N.; Caltabiano, R.; Musumeci, G. Immunolocalization of lubricin in the rat periodontal ligament during experimental tooth movement. *Acta Histochem.* **2012**, *114*, 700–704. [[CrossRef](#)]
12. Loreto, C.; Leonardi, R.; Musumeci, G.; Pannone, G.; Castorina, S. An ex vivo study on immunohistochemical localization of MMP-7 and MMP-9 in temporomandibular joint discs with internal derangement. *Eur. J. Histochem.* **2013**, *57*, e12. [[CrossRef](#)]
13. Musumeci, G.; Castrogiovanni, P.; Leonardi, R.; Trovato, F.M.; Szychlinska, A.; Di Giunta, A.; Loreto, C.; Castorina, S. New perspectives for articular cartilage repair treatment through tissue engineering: A contemporary review. *World J. Orthop.* **2014**, *18*, 80–88. [[CrossRef](#)]
14. Musumeci, G.; Trovato, F.M.; Loreto, C.; Leonardi, R.; Szychlinska, M.A.; Castorina, S.; Mobasher, A. Lubricin expression in human osteoarthritic knee meniscus and synovial fluid: A morphological, immunohistochemical and biochemical study. *Acta Histochem.* **2014**, *116*, 965–972. [[CrossRef](#)] [[PubMed](#)]
15. Cavuoti, S.; Matarese, G.; Isola, G.; Abdolreza, J.; Femiano, F.; Perillo, L. Combined orthodontic-surgical management of a transmigrated mandibular canine. *Angle Orthod.* **2016**, *86*, 681–691. [[CrossRef](#)] [[PubMed](#)]
16. Leonardi, R.; Perrotta, R.E.; Almeida, L.E.; Loreto, C.; Musumeci, G. Lubricin in synovial fluid of mild and severe temporomandibular joint internal derangements. *Med. Oral Patol. Oral Cir. Bucal.* **2016**, *21*, e793–e799. [[CrossRef](#)] [[PubMed](#)]
17. Szychlinska, M.A.; Trovato, F.M.; Di Rosa, M.; Malaguarnera, L.; Puzzo, L.; Leonardi, R.; Castrogiovanni, P.; Musumeci, G. Co-Expression and Co-Localization of Cartilage Glycoproteins CHI3L1 and Lubricin in Osteoarthritic Cartilage: Morphological, Immunohistochemical and Gene Expression Profiles. *Int. J. Mol. Sci.* **2016**, *17*, 359. [[CrossRef](#)]
18. Loreto, C.; Chiarenza, G.P.; Musumeci, G.; Castrogiovanni, P.; Imbesi, R.; Ruggeri, A.; Almeida, L.E.; Leonardi, R.; Leonardi, R. ADAM10 localization in temporomandibular joint disk with internal derangement: An ex vivo immunohistochemical study. *Acta Histochem.* **2016**, *118*, 293–298. [[CrossRef](#)]
19. Leonardi, R.; Perrotta, R.E.; Loreto, C.; Musumeci, G.; Crimi, S.; Dos Santos, J.N.; Rusu, M.C.; Bufo, P.; Barbato, E.; Pannone, G. Toll-like Receptor 4 Expression in the Epithelium of Inflammatory Periapical Lesions. An Immunohistochemical Study. *Eur. J. Histochem.* **2015**, *59*, 2547. [[CrossRef](#)]
20. Leonardi, R.; Lo Giudice, A.; Rugeri, M.; Muraglie, S.; Cordasco, G.; Barbato, E. Three-dimensional evaluation on digital casts of maxillary palatal size and morphology in patients with functional posterior crossbite. *Eur. J. Orthod.* **2018**, *40*, 556–562. [[CrossRef](#)]
21. Lo Giudice, A.; Fastuca, R.; Portelli, M.; Militi, A.; Bellocchio, M.; Spinuzza, P.; Briguglio, F.; Caprioglio, A.; Nucera, R. Effects of rapid vs slow maxillary expansion on nasal cavity dimensions in growing subjects: A methodological and reproducibility study. *Eur. J. Paediatr. Dent.* **2017**, *18*, 299–304. [[CrossRef](#)]
22. Koidis, P.T.; Zarifi, A.; Grigoriadou, E.; Garefis, P. Effect of age and sex on craniomandibular disorders. *J. Prosthet. Dent.* **1993**, *69*, 93–101. [[CrossRef](#)]
23. Leonardi, R.; Loreto, C.; Barbato, E.; Polimeni, A.; Caltabiano, R.; Lo Muzio, L. A histochemical survey of the human temporomandibular joint disc of patients with internal derangement without reduction. *J. Craniofac. Surg.* **2007**, *18*, 1429–1433. [[CrossRef](#)] [[PubMed](#)]
24. Cutroneo, G.; Piancino, M.G.; Ramieri, G.; Bracco, P.; Vita, G.; Isola, G.; Vermiglio, G.; Favalaro, A.; Anastasi, G.P.; Trimarchi, F. Expression of muscle-specific integrins in masseter muscle fibers during malocclusion disease. *Int. J. Mol. Med.* **2012**, *30*, 235–242. [[CrossRef](#)] [[PubMed](#)]
25. Almeida, L.E.; Pierce, S.; Zacharias, J.; Cullinan, W.; Noronha, L.; Olandoski, M.; Tramontina, V.; Loreto, C.; Leonardi, R. Immunohistochemical analysis of IL-1 beta in the discs of patients with temporomandibular joint dysfunction. *Cranio* **2017**, *35*, 233–237. [[CrossRef](#)]
26. Leonardi, R.; Muraglie, S.; Crimi, S.; Pirroni, M.; Musumeci, G.; Perrotta, R. Morphology of palatally displaced canines and adjacent teeth, a 3-D evaluation from cone-beam computed tomographic images. *BMC Oral Health* **2018**, *18*, 156. [[CrossRef](#)]

27. Almeida, L.E.; Hresko, K.; Sorenson, A.; Butcher, S.; Tayebi, L.; Leonardi, R.; Loreto, C.; Bosio, J.; Camejo, F.; Doetzer, A. Immunohistochemical expression of TLR-4 in temporomandibular joint dysfunction. *Cranio* **2019**, *37*, 323–328. [[CrossRef](#)]
28. Di Rosa, M.; Szychlińska, M.A.; Tibullo, D.; Malaguarnera, L.; Musumeci, G. Expression of CHI3L1 and CHIT1 in osteoarthritic rat cartilage model. A morphological study. *Eur. J. Histochem.* **2014**, *58*, 2423. [[CrossRef](#)]
29. Isola, G.; Polizzi, A.; Santonocito, S.; Alibrandi, A.; Ferlito, S. Expression of salivary and serum malondialdehyde and lipid profile of patients with periodontitis and coronary heart disease. *Int. J. Mol. Sci.* **2019**, *20*, 6061. [[CrossRef](#)]
30. Lo Giudice, A.; Ortensi, L.; Farronato, M.; Lucchese, A.; Lo Castro, A.; Isola, G. The step further smile virtual planning: Milled versus prototyped mock-ups for the evaluation of the designed smile characteristics. A comparative study in the aesthetic area using surface-to-surface matching technique. *BMC Oral Health* **2020**, *20*, 166.
31. Isola, G.; Alibrandi, A.; Pedulla, E.; Grassia, V.; Ferlito, S.; Perillo, L.; Rapisarda, E. Analysis of the effectiveness of lornoxicam and flurbiprofen on management of pain and sequelae following third molar surgery: A randomized, controlled, clinical trial. *J. Clin. Med.* **2019**, *8*, 325. [[CrossRef](#)]
32. Isola, G.; Matarese, G.; Alibrandi, A.; Dalessandri, D.; Migliorati, M.; Pedulla, E.; Rapisarda, E. Comparison of effectiveness of etoricoxib and diclofenac on pain and perioperative sequelae after surgical avulsion of mandibular third molars: A randomized, controlled, clinical trial. *Clin. J. Pain* **2019**, *35*, 908–915. [[CrossRef](#)] [[PubMed](#)]
33. Isola, G.; Perillo, L.; Migliorati, M.; Matarese, M.; Dalessandri, D.; Grassia, V.; Alibrandi, A.; Matarese, G. The impact of temporomandibular joint arthritis on functional disability and global health in patients with juvenile idiopathic arthritis. *Eur. J. Orthod.* **2019**, *41*, 117–124. [[CrossRef](#)]
34. Loreto, C.; Filetti, V.; Almeida, L.E.; La Rosa, G.R.M.; Leonardi, R.; Grippaudo, C.; Lo Giudice, A. MMP-7 and MMP-9 are overexpressed in the synovial tissue from severe temporomandibular joint dysfunction. *Eur. J. Histochem.* **2020**, *64*. [[CrossRef](#)] [[PubMed](#)]
35. Ferlazzo, N.; Curro, M.; Zinellu, A.; Caccamo, D.; Isola, G.; Ventura, V.; Carru, C.; Matarese, G.; Ientile, R. Influence of MTHFR genetic background on p16 and MGMT methylation in oral squamous cell cancer. *Int. J. Mol. Sci.* **2017**, *18*, 724. [[CrossRef](#)] [[PubMed](#)]
36. Puri, J.; Hutchins, B.; Bellinger, L.L.; Kramer, P.R. Estrogen and inflammation modulate estrogen receptor alpha expression in specific tissues of the temporomandibular joint. *Reprod. Biol. Endocrinol.* **2009**, *7*, 155. [[CrossRef](#)] [[PubMed](#)]
37. Papka, R.E.; Srinivasan, B.; Miller, K.E.; Hayashi, S. Localization of estrogen receptor protein and estrogen receptor messenger RNA in peripheral autonomic and sensory neurons. *Neuroscience* **1997**, *79*, 1153–1163. [[CrossRef](#)]
38. Wang, J.; Chao, Y.; Wan, Q.; Zhu, Z. The possible role of estrogen in the incidence of temporomandibular disorders. *Med. Hypotheses* **2008**, *71*, 564–567. [[CrossRef](#)]
39. Bettini, E.; Pollio, G.; Santagati, S.; Maggi, A. Estrogen receptor in rat brain: Presence in the hippocampal formation. *Neuroendocrinology* **1992**, *56*, 502–508. [[CrossRef](#)]
40. Castrogiovanni, P.; Trovato, F.M.; Szychlińska, M.A.; Nsir, H.; Imbesi, R.; Musumeci, G. The importance of physical activity in osteoporosis. From the molecular pathways to the clinical evidence. *Histol. Histopathol.* **2016**, *31*, 1183–1194. [[CrossRef](#)]
41. Helkimo, M. Studies on function and dysfunction of the masticatory system. 3. Analyses of anamnestic and clinical recordings of dysfunction with the aid of indices. *Swed. Dent. J.* **1974**, *67*, 165–181.
42. Lo Giudice, A.; Nucera, R.; Leonardi, R.; Paiusco, A.; Baldoni, M.; Caccianiga, G. A comparative assessment of the efficiency of orthodontic treatment with and without photobiomodulation during mandibular decrowding in young subjects: A single-center, single-blind randomized controlled trial. *Photobiomodul. Photomed. Laser Surg.* **2020**. [[CrossRef](#)] [[PubMed](#)]
43. Lo Giudice, A.; Nucera, R.; Perillo, L.; Paiusco, A.; Caccianiga, G. Is Low-level laser therapy an effective method to alleviate pain induced by active orthodontic alignment archwire? A Randomized clinical trial. *J. Evid. Based Dent. Pract.* **2019**, *19*, 71–78. [[CrossRef](#)] [[PubMed](#)]
44. Mayoral, V.A.; Espinosa, I.A.; Montiel, A.J. Association between signs and symptoms of temporomandibular disorders and pregnancy (case control study). *Acta Odontol. Latinoam.* **2013**, *26*, 3–7. [[PubMed](#)]

45. Woodrow, K.M.; Friedman, G.D.; Siegelau, A.B.; Collen, M.F. Pain tolerance: Differences according to age, sex and race. *Psychosom. Med.* **1972**, *34*, 548–556. [[CrossRef](#)] [[PubMed](#)]
46. Procacci, P.; Zoppi, M.; Maresca, M.; Romano, S. Studies on the pain threshold in man. *Adv. Neurol.* **1974**, *4*, 107–113.
47. Perillo, L.; Isola, G.; Esercizio, D.; Iovane, M.; Triolo, G.; Matarese, G. Differences in craniofacial characteristics in Southern Italian children from Naples: A retrospective study by cephalometric analysis. *Eur. J. Paediatr. Dent.* **2013**, *14*, 195–198.
48. Isola, G.; Alibrandi, A.; Rapisarda, E.; Matarese, G.; Williams, R.C.; Leonardi, R. Association of vitamin D in patients with periodontitis: A cross-sectional study. *J. Periodontal Res.* **2020**. [[CrossRef](#)]
49. Isola, G.; Giudice, A.L.; Polizzi, A.; Alibrandi, A.; Patini, R.; Ferlito, S. Periodontitis and tooth loss have negative systemic impact on circulating progenitor cell levels: A Clinical study. *Genes* **2019**, *10*, 1022. [[CrossRef](#)]
50. Isola, G.; Matarese, G.; Ramaglia, L.; Pedulla, E.; Rapisarda, E.; Iorio-Siciliano, V. Association between periodontitis and glycosylated haemoglobin before diabetes onset: A cross-sectional study. *Clin. Oral Investig.* **2019**. [[CrossRef](#)]
51. Isola, G.; Polizzi, A.; Alibrandi, A.; Indelicato, F.; Ferlito, S. Analysis of Endothelin-1 Concentrations in individuals with periodontitis. *Sci. Rep.* **2020**, *10*, 1652. [[CrossRef](#)]
52. Isola, G.; Polizzi, A.; Muraglie, S.; Leonardi, R.; Lo Giudice, A. Assessment of Vitamin C and Antioxidant profiles in saliva and serum in patients with periodontitis and ischemic heart disease. *Nutrients* **2019**, *11*, 2956. [[CrossRef](#)] [[PubMed](#)]
53. Curro, M.; Matarese, G.; Isola, G.; Caccamo, D.; Ventura, V.P.; Cornelius, C.; Lentini, M.; Cordasco, G.; Ientile, R. Differential expression of transglutaminase genes in patients with chronic periodontitis. *Oral Dis.* **2014**, *20*, 616–623. [[CrossRef](#)] [[PubMed](#)]
54. Briguglio, F.; Briguglio, E.; Briguglio, R.; Cafiero, C.; Isola, G. Treatment of infrabony periodontal defects using a resorbable biopolymer of hyaluronic acid: A randomized clinical trial. *Quintessence Int.* **2013**, *44*, 231–240. [[CrossRef](#)] [[PubMed](#)]
55. Lupton, D.E. Psychological aspects of temporomandibular joint dysfunction. *J. Am. Dent. Assoc.* **1969**, *79*, 131–136. [[CrossRef](#)]
56. Molin, C.; Schalling, D.; Edman, G. Psychological studies of patients with mandibular pain dysfunction syndrome. 1. Personality traits in patients and controls. *Sven. Tandlak. Tidskr.* **1973**, *66*, 1–13.
57. Matarese, G.; Curro, M.; Isola, G.; Caccamo, D.; Vecchio, M.; Giunta, M.L.; Ramaglia, L.; Cordasco, G.; Williams, R.C.; Ientile, R. Transglutaminase 2 up-regulation is associated with RANKL/OPG pathway in cultured HPDL cells and THP-1-differentiated macrophages. *Amino Acids* **2015**, *47*, 2447–2455. [[CrossRef](#)]
58. Reiter, S.; Eli, I.; Mahameed, M.; Emodi-Perlman, A.; Friedman-Rubin, P.; Reiter, M.A.; Winocur, E. Pain catastrophizing and pain persistence in temporomandibular disorder patients. *J. Oral Facial Pain Headache* **2018**, *32*, 309–320. [[CrossRef](#)]
59. Musumeci, G.; Magro, G.; Cardile, V.; Coco, M.; Marzagalli, R.; Castrogiovanni, P.; Imbesi, R.; Graziano, A.C.; Barone, F.; Di Rosa, M.; et al. Characterization of matrix metalloproteinase-2 and -9, ADAM-10 and N-cadherin expression in human glioblastoma multiforme. *Cell Tissue Res.* **2015**, *362*, 45–60. [[CrossRef](#)]
60. Piancino, M.G.; Isola, G.; Cannavale, R.; Cutroneo, G.; Vermiglio, G.; Bracco, P.; Anastasi, G.P. From periodontal mechanoreceptors to chewing motor control: A systematic review. *Arch. Oral Biol.* **2017**, *78*, 109–121. [[CrossRef](#)]
61. Matarese, G.; Isola, G.; Anastasi, G.P.; Favaloro, A.; Milardi, D.; Vermiglio, G.; Vita, G.; Cordasco, G.; Cutroneo, G. Immunohistochemical analysis of TGF-beta1 and VEGF in gingival and periodontal tissues: A role of these biomarkers in the pathogenesis of scleroderma and periodontal disease. *Int. J. Mol. Med.* **2012**, *30*, 502–508. [[CrossRef](#)]
62. Lo Giudice, A.; Caccianiga, G.; Crimi, S.; Cavallini, C.; Leonardi, R. Frequency and type of ponticulus posticus in a longitudinal sample of nonorthodontically treated patients: Relationship with gender, age, skeletal maturity, and skeletal malocclusion. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2018**, *126*, 291–297. [[CrossRef](#)] [[PubMed](#)]
63. Sassarini, D.J. Depression in midlife women. *Maturitas* **2016**, *94*, 149–154. [[CrossRef](#)] [[PubMed](#)]
64. Iwasaki, L.R.; Gonzalez, Y.M.; Liu, Y.; Liu, H.; Markova, M.; Gallo, L.M.; Nickel, J.C. TMJ energy densities in healthy men and women. *Osteoarthr. Cartil.* **2017**, *25*, 846–849. [[CrossRef](#)] [[PubMed](#)]

65. Huhtela, O.S.; Nääpänkangas, R.; Joensuu, T.; Raustia, A.; Kunttu, K.; Sipilä, K. Self-Reported Bruxism and symptoms of temporomandibular disorders in Finnish University students. *J. Oral Facial Pain Headache* **2016**, *30*, 311–317. [[CrossRef](#)]
66. Isola, G.; Matarese, M.; Briguglio, F.; Grassia, V.; Picciolo, G.; Fiorillo, L.; Matarese, G. Effectiveness of Low-Level Laser Therapy during Tooth Movement: A Randomized Clinical Trial. *Materials* **2019**, *12*, 2187. [[CrossRef](#)]
67. Vannuccini, S.; Bocchi, C.; Severi, F.M.; Challis, J.R.; Petraglia, F. Endocrinology of human parturition. *Ann. D'endocrinologie* **2016**, *77*, 105–113. [[CrossRef](#)]
68. Isola, G.; Matarese, M.; Ramaglia, L.; Cicciu, M.; Matarese, G. Evaluation of the efficacy of celecoxib and ibuprofen on postoperative pain, swelling, and mouth opening after surgical removal of impacted third molars: A randomized, controlled clinical trial. *Int. J. Oral Maxillofac. Surg.* **2019**, *48*, 1348–1354. [[CrossRef](#)]
69. Goh, W.A.; Zalud, I. Placenta accreta: Diagnosis, management and the molecular biology of the morbidly adherent placenta. *J. Matern. Fetal Neonatal Med.* **2016**, *29*, 1795–1800. [[CrossRef](#)]
70. Matarese, G.; Isola, G.; Ramaglia, L.; Dalessandri, D.; Lucchese, A.; Alibrandi, A.; Fabiano, F.; Cordasco, G. Periodontal biotype: Characteristic, prevalence and dimensions related to dental malocclusion. *Minerva Stomatol.* **2016**, *65*, 231–238.
71. Cannavale, R.; Matarese, G.; Isola, G.; Grassia, V.; Perillo, L. Early treatment of an ectopic premolar to prevent molar-premolar transposition. *Am. J. Orthod. Dentofac. Orthop.* **2013**, *143*, 559–569. [[CrossRef](#)]
72. Isola, G.; Matarese, M.; Ramaglia, L.; Iorio-Siciliano, V.; Cordasco, G.; Matarese, G. Efficacy of a drug composed of herbal extracts on postoperative discomfort after surgical removal of impacted mandibular third molar: A randomized, triple-blind, controlled clinical trial. *Clin. Oral Investig.* **2019**, *23*, 2443–2453. [[CrossRef](#)] [[PubMed](#)]
73. Leonardi, R.; Almeida, L.E.; Trevilatto, P.C.; Loreto, C. Occurrence and regional distribution of TRAIL and DR5 on temporomandibular joint discs: Comparison of disc derangement with and without reduction. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2010**, *109*, 244–251. [[CrossRef](#)] [[PubMed](#)]
74. Matarese, G.; Isola, G.; Anastasi, G.P.; Cutroneo, G.; Favalaro, A.; Vita, G.; Cordasco, G.; Milardi, D.; Zizzari, V.L.; Tetè, S.; et al. Transforming Growth Factor Beta 1 and Vascular Endothelial Growth Factor levels in the pathogenesis of periodontal disease. *Eur. J. Inflamm.* **2013**, *11*, 479–488. [[CrossRef](#)]
75. Trenti, A.; Tedesco, S.; Boscaro, C.; Trevisi, L.; Bolego, C.; Cignarella, A. Estrogen, Angiogenesis, immunity and cell metabolism: Solving the puzzle. *Int. J. Mol. Sci.* **2018**, *19*, 859. [[CrossRef](#)]
76. Isola, G.; Anastasi, G.P.; Matarese, G.; Williams, R.C.; Cutroneo, G.; Bracco, P.; Piancino, M.G. Functional and molecular outcomes of the human masticatory muscles. *Oral Dis.* **2018**, *24*, 1428–1441. [[CrossRef](#)] [[PubMed](#)]
77. Lo Muzio, L.; Campisi, G.; Farina, A.; Rubini, C.; Pastore, L.; Giannone, N.; Colella, G.; Leonardi, R.; Carinci, F. Effect of p63 expression on survival in oral squamous cell carcinoma. *Cancer Investig.* **2007**, *25*, 464–469. [[CrossRef](#)]
78. Isola, G.; Alibrandi, A.; Curro, M.; Matarese, M.; Ricca, S.; Matarese, G.; Ientile, R.; Kocher, T. Evaluation of salivary and serum ADMA levels in patients with periodontal and cardiovascular disease as subclinical marker of cardiovascular risk. *J. Periodontol.* **2020**. [[CrossRef](#)]
79. Aufdemorte, T.B.; Van Sickels, J.E.; Dolwick, M.F.; Sheridan, P.J.; Holt, G.R.; Aragon, S.B.; Gates, G.A. Estrogen receptors in the temporomandibular joint of the baboon (*Papio cynocephalus*): An autoradiographic study. *Oral Surg. Oral Med. Oral Pathol.* **1986**, *61*, 307–314. [[CrossRef](#)]
80. Perillo, L.; Padricelli, G.; Isola, G.; Femiano, F.; Chiodini, P.; Matarese, G. Class II malocclusion division 1: A new classification method by cephalometric analysis. *Eur. J. Paediatr. Dent.* **2012**, *13*, 192–196.
81. Sorenson, A.; Hresko, K.; Butcher, S.; Pierce, S.; Tramontina, V.; Leonardi, R.; Loreto, C.; Bosio, J.; Almeida, L.E. Expression of Interleukin-1 and temporomandibular disorder: Contemporary review of the literature. *Cranio* **2018**, *36*, 268–272. [[CrossRef](#)]
82. Isola, G.; Polizzi, A.; Iorio-Siciliano, V.; Alibrandi, A.; Ramaglia, L.; Leonardi, R. Effectiveness of a nutraceutical agent in the non-surgical periodontal therapy: A randomized, controlled clinical trial. *Clin. Oral Investig.* **2020**, in press 7 June.
83. Nucera, R.; Militi, A.; Lo Giudice, A.; Longo, V.; Fastuca, R.; Caprioglio, A.; Cordasco, G.; Papadopoulos, M.A. Skeletal and Dental Effectiveness of Treatment of Class II Malocclusion With Headgear: A Systematic Review and Meta-analysis. *J. Evid. Based. Dent. Pract.* **2018**, *18*, 41–58. [[CrossRef](#)] [[PubMed](#)]

84. Fiorillo, L. Spine and TMJ: A Pathophysiology report. *J. Funct. Morphol. Kinesiol.* **2020**, *5*, 24. [[CrossRef](#)]
85. Fiorillo, L.; Musumeci, G. TMJ Dysfunction and Systemic Correlation. *J. Funct. Morphol. Kinesiol.* **2020**, *5*, 20. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).