Assessment of Pain Sensitivity in Patients with Deep Bite and Sex- and Age-Matched Controls

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Aims: *To compare pain sensitivity between deep bite patients and a sex- and age-matched control group with normal occlusion.* ***Methods:*** *Pain sensitivity was assessed by injections of the excitatory amino acid glutamate into the masseter and brachioradialis muscles. Intensity of glutamate-evoked pain was scored by the subjects (n = 60) on a 0 to 10 cm visual analog scale. Subjects drew the perceived pain area on a face and arm chart and described the quality of pain on the McGill Pain Questionnaire. Thresholds for cold detection, cold pain, cold tolerance, warmth detection, heat pain, and heat tolerance were assessed on the masseter and brachioradialis muscles. Pressure pain threshold and pain tolerance threshold were determined on the temporomandibular joint, masseter, anterior temporalis, and brachioradialis muscles. The differences between groups, age, and gender were tested by two-way ANOVA, and the significant differences were then tested for the effect of the presence of temporomandibular disorder (TMD) by linear regression.* ***Results:*** *Glutamate-evoked pain intensity was significantly different between groups with no gender differences. Quality of pain did not vary between groups, but significant gender-related differences were observed. Significant differences in thermal sensitivity between groups and gender were found, whereas mechanical sensitivity did not vary between groups but between genders. None of the significant differences were due to the effect of TMD.* ***Conclusion:*** *These data provide further evidence of gender-related differences in somatosensory sensitivity and for the first time indicate that subjects with deep bite may be more sensitive to glutamate-evoked pain and thermal stimuli.* J OROFAC PAIN 2011;25:15–24

Key words: deep bite, occlusion, orofacial pain, quantitative sensory testing, trigeminal physiology

From a clinical point of view, it is important to understand the relationship between occlusal variables and craniofacial pain, which have been studied and discussed for decades.[1] Many studies have found no associations between temporomandibular disorders (TMD) and deep bite,[2–11] whereas others have shown an association between TMD signs and symptoms and deep bite.[12–15]

Recently, TMD and psychological status were examined in adult patients with a deep bite who were referred for treatment and compared with an age- and sex-matched adult control group with normal occlusion.[15] The study found that tension-type headache, muscle disorders, disc displacement, and other joint disorders occurred significantly more often in the deep bite group compared with the control group. Also, somatization scores were significantly higher in the deep bite group. These findings suggest an association between deep bite and TMD in patients referred for orthodontic treatment.

From a neurobiological perspective, both peripheral and central sensitization processes have been implicated in the pathophysiology of myofascial TMD and tension-type headache.[16–22] Patients with myofascial TMD pain generally have lower thresholds to mechanical stimuli applied to the painful area when compared to control subjects.[23,24] However, it has also been shown that myofascial TMD patients have decreased pain thresholds outside the painful area and have a greater temporal summation or aftersensation of nociceptive cutaneous input, indicating a more generalized hyperexcitability or hypervigiliance.[25–29]

Intramuscular injection of hypertonic saline into the masseter muscles causes deep localized pain around the injection site, as well as spreading and referral of pain to the temple, teeth, and ear in healthy control subjects. In addition to hypertonic saline, other algesic substances can be used to induce experimental muscle pain, eg, the excitatory amino acid glutamate, which has been used in several recent studies[30–32] and which may mimic some of the characteristics of TMD pain.[33] When patients with myofascial TMD pain are provoked with this type of longer-lasting painful input, they experience significantly more pain and in a larger area compared to control subjects.[30,31,33] The same technique has also been used in patients with frequent episodic and chronic tension-type headache, and both groups have significantly more pain and significantly larger pain areas when compared to healthy controls.[34] Therefore, TMD has been suggested to be a complex disease based on multiple gene x environment interactions leading to significant perturbation of the somatosensory function[35] and influenced by gender-differences in pain sensitivity.[27,36–38]

In the present study, it was hypothesized that if deep bite is associated with TMD pain, it would be expected that patients with deep bites are also more sensitive to painful stimulation in a gender-dependent manner. The aim of the present study was therefore to compare pain sensitivity between patients with deep bite and a sex- and age-matched control group with normal occlusion.

Materials and Methods

Subjects

The sample comprised 60 adults: 30 patients with deep bite (deep bite group) and 30 subjects with normal occlusion (control group). None of the adults in either group had craniofacial anomalies or systemic muscle or joint disorders, and none of the adults were referred for TMD treatment. Symptoms and signs of TMD according to the Research Diagnostic Criteria for TMD (RDC/TMD, Axis I, ie, muscle disorders, disc displacement, and joint disorders) in the same groups of patients have previously been reported by Sonnesen and Svensson.[15]

The deep bite group consisted of 20 females, aged 22 to 42 years (mean 30.3 years), and 10 males, aged 23 to 43 years (mean 33.1 years), admitted for orthodontic treatment to the Department of Orthodontics, School of Dentistry, Aarhus University, Denmark. Patients who had at least 24 permanent teeth present and who had applied for orthodontic treatment in the period from March 2002 to December 2003 were included in the study. The Sonnesen and Svensson study showed that muscle disorders occurred in 50% of the females and 20% of the males, disc displacement occurred in 25% of the females and in 40% of the males, and other joint disorders occurred in 35% of the females.[15]

The control group consisted of 20 females, aged 23 to 40 years (mean 29.4 years), and 10 males, aged 25 to 44 years (mean 34.2 years), with normal occlusion or minor malocclusion that did not require orthodontic treatment according to the Danish procedure for screening the population for malocclusions entailing health risks.[39] The control group was selected from either students or staff at the School of Dentistry and were matched to the deep bite group according to age (± 1 year) and gender. The Sonnesen and Svensson study showed that none of the controls had muscle disorders or joint disorders and that disc displacement occurred in 10% of the females.[15]

The study was approved by the Ethical Committee for Aarhus County, Denmark (Reference no. 20020040), and each participant signed an informed consent before inclusion, in accordance with the Helsinki declaration.

Study Design

Pain sensitivity was assessed by injections of the excitatory amino acid glutamate into a jaw muscle (masseter) and an arm muscle (brachioradialis). The pain intensity was scored by the subjects on an electronic 0 to 10 cm visual analog scale (VAS) for 15 minutes, and the subjects were asked to draw the perceived area of pain on charts of the face and arm (pain areas) and to describe the quality of pain in a Danish version of the McGill Pain Questionnaire (MPQ).[40] Furthermore, thermal sensitivity was tested. Cold detection threshold (CDT), cold pain threshold (CPT), cold tolerance threshold (CTT), warmth detection threshold (WDT), heat pain threshold (HPT), and heat tolerance thresh-

old (HTT) were assessed on the skin overlying the masseter and brachioradialis muscles. Pressure pain threshold (PPT) and pain tolerance threshold (PTT) were determined on the temporomandibular joint (TMJ), the masseter, the anterior temporalis, and the brachioradialis muscles. Thermal and mechanical sensitivity was assessed before the glutamate injections (baseline). One of the authors (LS) performed all of the recordings prior to orthodontic treatment of the deep bite group.

Glutamate-Evoked Pain

To evoke muscle pain, 0.2 mL glutamate (1.0 M) was injected into the deep masseter muscle.[41] The injection was given manually (with a 27-gauge hypodermic needle and disposable syringe) into the right deep masseter muscle midway between its upper and lower border and 1 cm posterior to its anterior border. The needle penetrated the skin and the masseter muscle until bone contact was perceived (usually 1 to 2 cm insertion; touching the underlying mandibular bone also typically generated a distinct sensation from the subject). The needle was then withdrawn about 2 mm, and the glutamate was injected after aspiration.[24] To evoke pain outside the trigeminal region, 0.4 mL glutamate (1.0 M) was injected into the right brachioradialis muscle. After each injection, the subjects continuously scored the pain intensity for up to 15 minutes on the 10-cm electronic VAS with the lower extreme marked "no pain" and the upper extreme marked "most pain imaginable." The VAS signals were sampled every 5 seconds and stored on a personal computer. Fifteen minutes after the injections, the subjects described the quality of the glutamate-evoked pain on the MPQ and drew the distribution of pain on diagrams of the face and arm. The drawings were then digitized (ACECAD, model D9000+ digitizer) to calculate the area of perceived pain in arbitrary units (au). Peak pain was measured as the peak VAS score, the area under the VAS curve (VASauc) was measured to obtain a measure of the overall amount of pain, and the onset and offset of pain were determined from the VAS time profiles. The pain rating indices for the sensory, PRI(S); affective, PRI(A); evaluative, PRI(E); and miscellaneous, PRI(M), dimensions of pain were calculated from the MPQ, in accordance with previous descriptions.[30,42]

Assessment of Thermal and Mechanical Sensitivity

Before injection of glutamate (baseline), CDT, CPT, CTT, WDT, HPT, HTT, PPT, and PTT were determined.

A thermal stimulator (TSA II Neurosensory Analyzer, Medoc) with a 3 × 3-cm probe based on the Peltier principle was used to assess sensitivity to superficial, phasic stimuli applied to the skin above the masseter muscles bilaterally and the right brachioradialis muscle. CDT and WDT were defined as the temperature (°C) at which the subject first perceived the thermal stimulus as cold or hot. CPT and HPT were defined as the temperature at which the subject first perceived the thermal stimulus as painful. CTT and HTT were defined as the temperature at which the subject could not tolerate any more cold or heat with cutoffs at 0°C and 50°C, respectively. The subject pushed a button to stop the decrease or increase in temperature. The baseline temperature of the thermode was set at 30°C and decreased or increased by 2°C/sec. The mean value of three repeated CDT, WDT, CPT, HPT, CTT, HTT was used for further analysis.[43,44]

A pressure algometer (Somedic) was used to test the sensitivity to deep, phasic mechanical stimuli applied to the TMJs bilaterally, the masseter and anterior temporalis muscles bilaterally, and the right brachioradialis muscle. PPT was defined as the amount of pressure (kPa) the subject first perceived as painful.[24] PTT was defined as the maximal amount of pressure (kPa) the subject could tolerate. The subject pushed a button to stop the pressure stimulation when the threshold was reached. PPTs were determined twice and PTTs once to avoid sensitization with a constant application rate of 30 kPa/second and a probe diameter of 1 cm. The mean value of PPTs was used for further statistical evaluation.

Statistical Methods

Normality of the distributions was assessed by parameters of skewness and kurtosis and by the Shapiro-Wilks W-test. Differences between the groups, age, and gender were tested by the ANOVA two-way analysis. Significant differences were then tested for the possible effect of the presence of TMD by linear regression analysis. The results were considered to be significant at values below $P < .05$. The statistical analyses were performed using the SPSS 13 Statistical Program Package (IBM).

Results

Glutamate-Evoked Pain

Injection of glutamate into the masseter muscle evoked moderate to strong pain in all subjects. Significant differences between the two groups were observed for VAS peak pain scores and VASauc. The

Table 1 Pain Onset, Pain Offset, Peak Pain, VASauc, and Area of Perceived Pain from Face Drawings in the Deep Bite and Control Groups Following Glutamate Injection into the Masseter and Brachioradialis Muscles

	Deep bite		Control		
	Female mean (SD)	Male mean (SD)	Female mean (SD)	Male mean (SD)	*P*
Masseter					
Pain onset (s)	4.9 (5.5)	3.5 (4.6)	6.8 (7.0)	6.2 (6.2)	NS
Pain offset (s)	606.7 (238.4)	621.0 (199.4)	621.5 (154.2)	524.2 (203.8)	NS
Peak pain (cm)	6.1 (2.2)	6.1 (2.6)	4.5 (2.4)	3.9 (2.0)	*
VASauc (cm*s)	2121.9 (1458.3)	1698.8 (790.7)	1490.9 (710.8)	1306.2 (891.8)	**
Perceived area (au)	418.4 (603.8)	8.2 (3.9)	292.9 (434.1)	4.5 (2.9)	***
Brachioradialis					
Pain onset (s)	19.7 (37.9)	8.9 (11.5)	12.2 (12.3)	18.7 (33.7)	NS
Pain offset (s)	552.2 (230.2)	455.0 (110.9)	555.3 (210.2)	434.8 (145.2)	NS
Peak pain (cm)	4.8 (2.6)	3.9 (1.6)	4.1 (2.4)	3.4 (2.2)	NS
VASauc (cm*s)	1435.6 (1074.3)	1015.3 (521.2)	1469.8 (127.8)	1027.1 (904.9)	NS
Perceived area (au)	762.9 (1115.9)	9.9 (10.3)	269.3 (309.0)	4.7 (4.5)	***

*$P < .01$, significant difference between groups (ANOVA).
**$P < .05$, significant difference between groups (ANOVA).
***$P < .001$, significant difference between gender (ANOVA).
NS: no significant difference between groups, gender, or age.

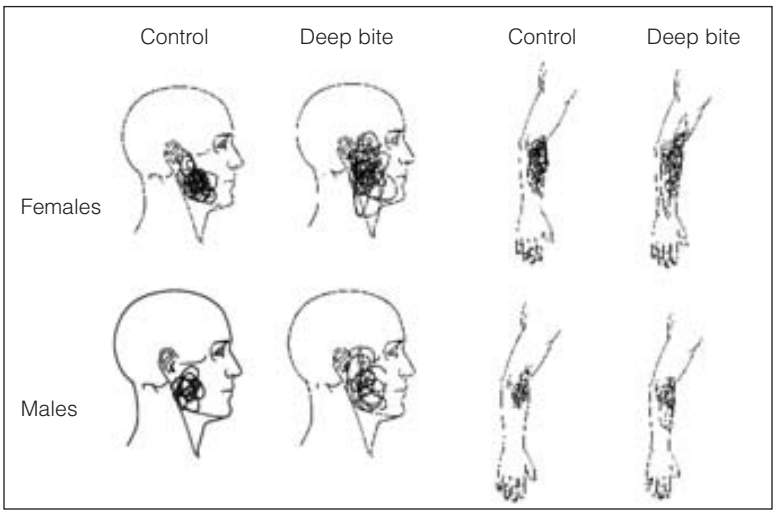

Fig 1 Perceived area of glutamate-evoked pain in the masseter and brachioradialis muscles in the deep bite group and in control group.

VAS peak pain score was higher ($P < .01$, Table 1) and the VASauc was larger ($P < .05$, Table 1) in the deep bite group than in the control group. No significant differences were found between the groups for glutamate-evoked pain in the brachioradialis muscle (Table 1).

The perceived areas of glutamate-evoked pain in the masseter and brachioradialis muscles are shown in Fig 1 and Table 1. The perceived area of glutamate-evoked pain in the masseter and brachioradialis muscles was significantly larger in females than in males ($P < .001$, Table 1). However, there were no significant differences between the groups (Table 1).

The qualitative description of glutamate-evoked pain is shown in Table 2. PRI(S), PRI(A), PRI(E), and PRI(M) derived from the MPQ showed no significant differences between the two groups for glutamate-evoked pain in the masseter muscle. A significant gender difference was found for glutamate-evoked pain in the brachioradialis muscle: PRI(S) was significantly higher in females than in males ($P < .05$).

The significant differences in the glutamate-evoked pain were not due to the effect of TMD.

Table 2 Pain Rating Indices (PRI) for Sensory (S), Affective (A), Evaluative (E), and Miscellaneous (M) Dimensions of Pain Evoked by Glutamate Injection into Masseter and Brachioradialis Muscles in the Deep Bite and Control Groups

	Deep bite		Control		
	Female mean (SD)	Male mean (SD)	Female mean (SD)	Male mean (SD)	*P*
Masseter					
PRI(S)	20.4 (13.1)	10.9 (8.3)	16.3 (11.8)	12.9 (8.8)	NS
PRI(A)	2.9 (4.4)	1.0 (1.7)	1.6 (2.8)	1.0 (1.5)	NS
PRI(E)	2.6 (2.1)	1.5 (1.8)	2.0 (2.5)	1.4 (2.1)	NS
PRI(M)	6.3 (4.3)	4.4 (4.8)	4.4 (6.0)	3.7 (4.1)	NS
Brachioradialis					
PRI(S)	15.7 (6.4)	8.3 (4.3)	14.7 (11.7)	9.6 (7.9)	*
PRI(A)	1.2 (2.4)	0.4 (0.7)	0.5 (1.1)	0.7 (1.9)	NS
PRI(E)	1.4 (1.9)	1.1 (1.4)	1.5 (1.9)	1.3 (1.9)	NS
PRI(M)	4.9 (5.3)	1.7 (1.8)	3.7 (4.6)	3.5 (4.2)	NS

* = $P < .05$, significant difference between gender (ANOVA)
NS: no significant difference between groups, gender, or age

Thermal and Mechanical Sensitivity

CDT, WDT, CPT, HPT, CTT, and HTT values are shown in Figs 2 and 3. The CTT determined on the masseter muscle was significantly higher in the deep bite group when compared to the control group and significantly higher in the females than in males ($P < .05$) (Fig 2). HTT determined on the masseter muscle was significantly lower in the deep bite group when compared to the control group and significantly lower in females than in males ($P < .05$) (Fig 3). The HPT determined on the masseter muscle was significantly lower in females than in males ($P < .05$). In the brachioradialis muscle, the CPT and the CTT were significantly higher in females than in males ($P < .05$), and the HTT was significantly lower in females than in males ($P < .001$). The significant differences in the thermal sensitivity were not due to effect of TMD.

PPT and PTT values are shown in Fig 4. The PPT and the PTT determined on the TMJ and on the masseter, anterior temporalis, and the brachioradialis muscles showed no significant difference between the two groups. The PPTs determined on the masseter muscle ($P < .001$), anterior temporalis ($P < .05$), the TMJ ($P < .05$), and the brachioradialis muscle ($P < .05$) were significantly higher in males than in females. The PTTs determined on the masseter muscle ($P < .05$), anterior temporalis ($P < .05$), the TMJ ($P < .001$), and the brachioradialis muscle ($P < .05$) were significantly higher in males than in females. The significant differences in mechanical sensitivity were not due to the effect of TMD.

Discussion

Overall, the new findings in this study indicate that subjects with a deep bite may be more pain sensitive and may have disturbances in the somatosensory processing of thermal stimuli. This has not previously been reported in the literature.

In the present study, significant differences in pain sensitivity were found between genders. Thus, the quality of pain and thermal and mechanical sensitivity were significantly different between genders. Within those parameters, females showed a higher somatosensory sensitivity than males. These findings are in general agreement with previous studies performed on patients with TMD where gender differences in pain sensitivity have been described.[27,36,37]

One potential confounding factor in the present study stemmed from a previous study where it was found that subjects with deep bite were more likely to suffer from a TMD or headache problem.[15] In this previous study, tension headache, muscle disorders, disc displacement, and other joint disorders were found to occur significantly more often in the deep bite group compared with the controls, and there were no gender differences. Also, somatization scores were significantly higher in the deep bite group compared with the controls.[15] Therefore, significant differences in glutamate-evoked pain and significant differences in thermal and mechanical sensitivity were tested for the possible effect of TMD in the present study. None of the significant differences in the present study was due to the effect of TMD. The significant differences

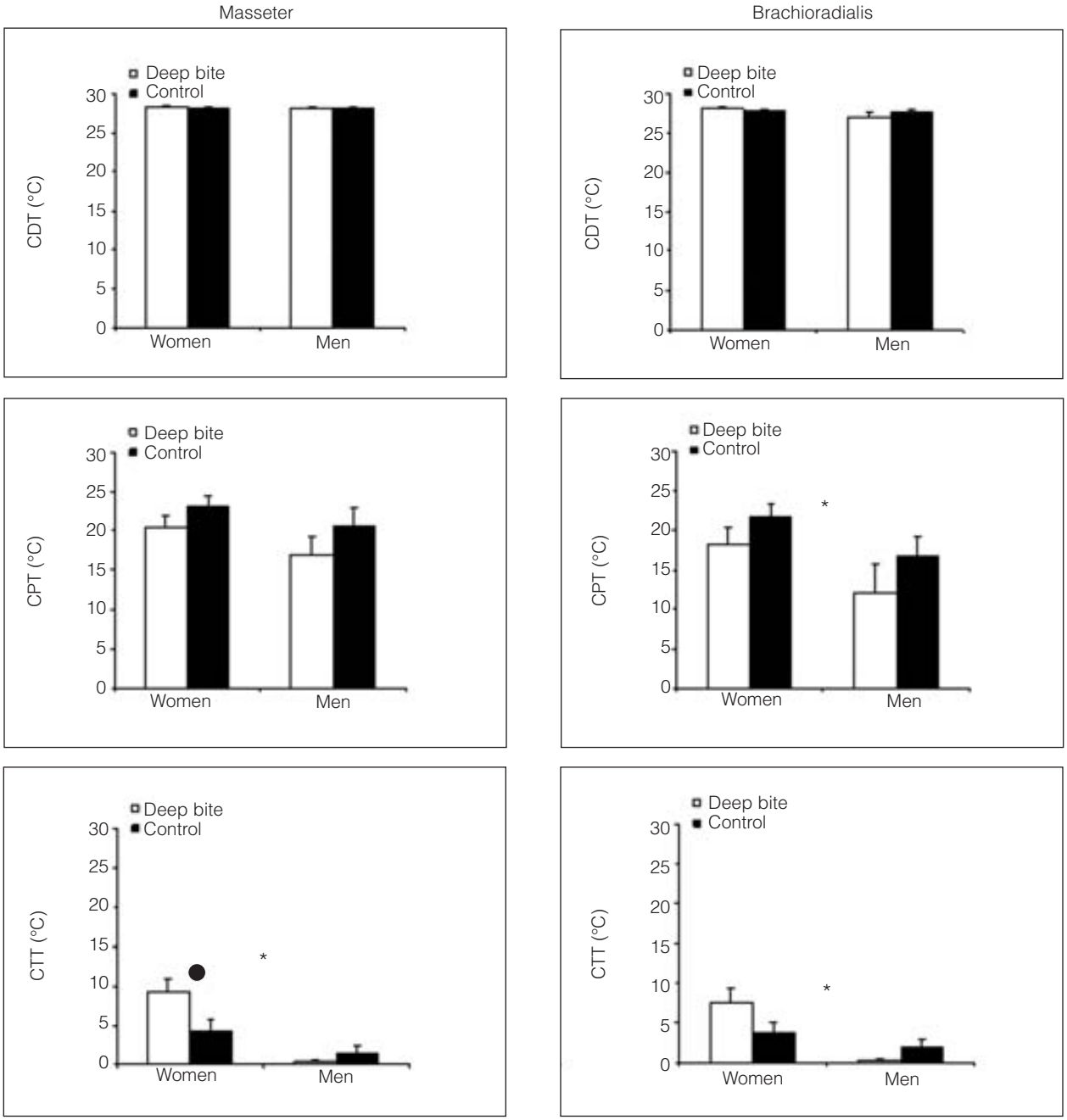

Fig 2 Mean values and standard error of the mean for CDT, CPT, and CTT in the masseter and brachioradialis muscles in the deep bite group and in the control group. Black dot (●) indicates significant differences between the deep bite group and control group ($P < .05$, ANOVA). Asterisks indicate significant differences between genders (* = $P < .05$, ANOVA).

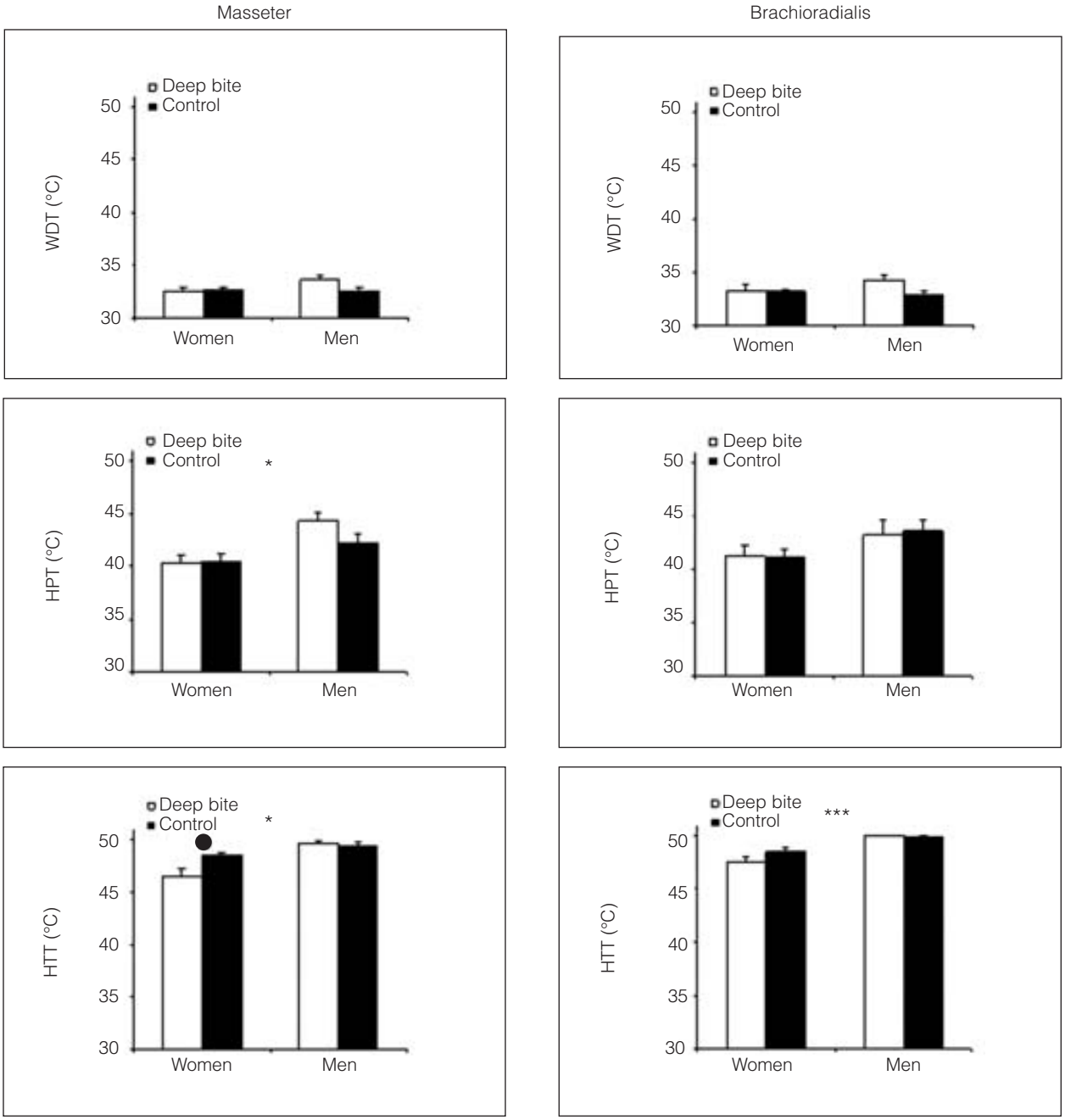

Fig 3 Mean values and standard error of the mean for WDT, HPT, and HTT in the masseter and brachioradialis muscles in the deep bite group and in the control group. Black dot (●) indicates significant differences between the deep bite group and control group ($P < .05$, ANOVA). Asterisks indicate significant differences between genders (* = $P < .05$; *** = $P < .001$, ANOVA).

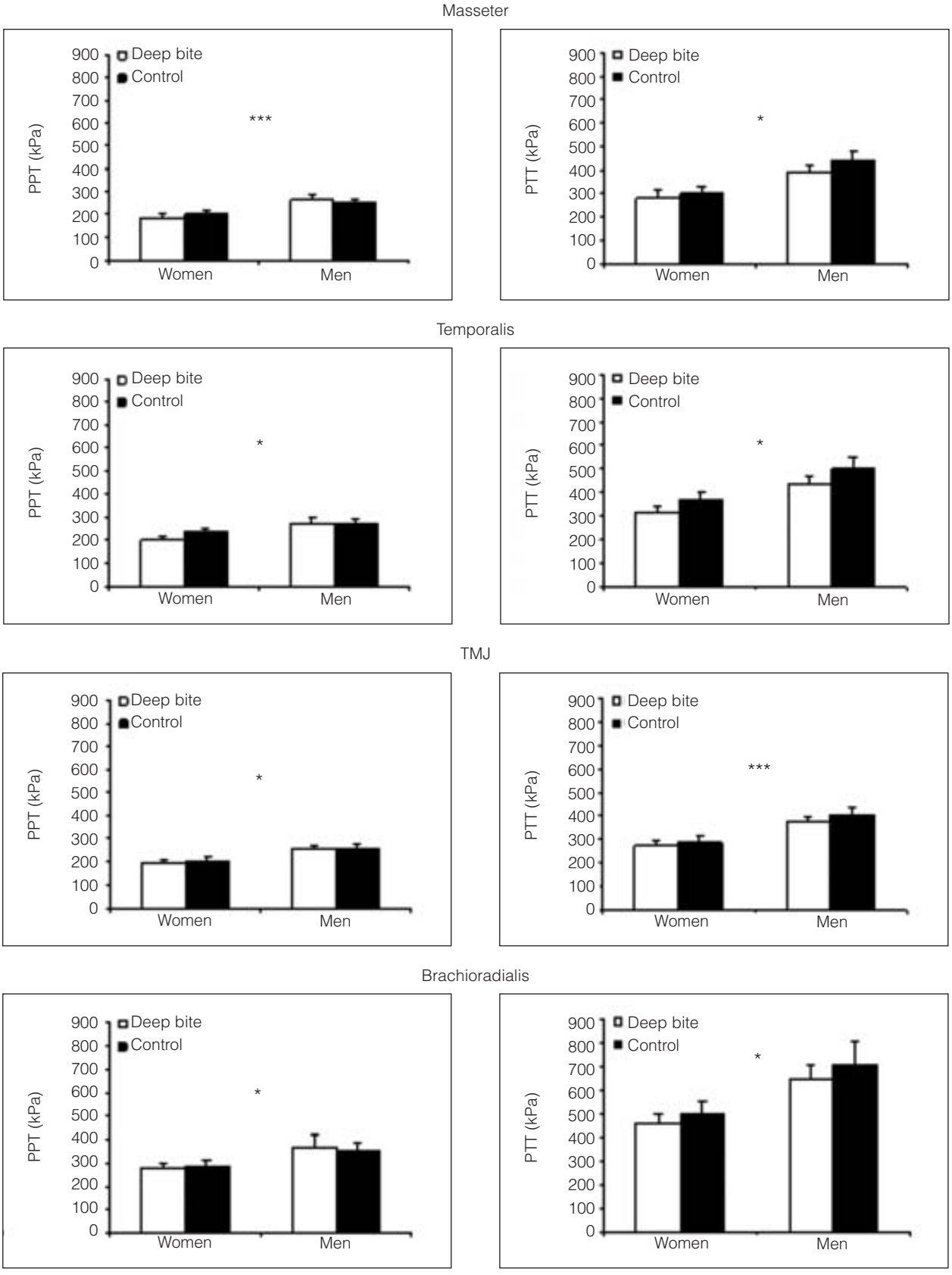

Fig 4 Mean values and standard error of the mean for PPT *(left column)* and PTT *(right column)* in the masseter, anterior temporalis, TMJ, and brachioradialis in the deep bite group and in the control group. No significant differences between the deep bite group and the control group were found. Asterisks indicate significant differences between genders (* = $P > .05$; *** = $P < .001$, ANOVA).

in somatosensory sensitivity were due to the effect of the deep bite and gender.

With regard to cutaneous measures, the present study demonstrated that subjects with a deep bite may be more sensitive to glutamate-evoked pain and thermal stimuli. These findings indicate that both occlusal risk factors and general pain sensitivity, perhaps genetically determined, would lead to a greater risk of developing TMD. A recent 3-year prospective study demonstrated that individuals who developed TMD also had a higher prevalence of joint, back, chest, and menstrual pain at baseline compared to individuals who did not develop TMD pain.[45] Indeed, causal interferences cannot be analyzed in a cross-sectional study. Still, the present study suggests a complex interaction between deep bite and pain sensitivity, which could be related to specific genotypes. This suggestion would be in accordance with the current view that TMD is a complex type of pain determined by multiple gene x environment interactions.[35] The present findings come from an age- and gender-matched cross-sectional study that used robust thermal and mechanical sensitivity measurements and a well-established experimental pain model for prolonged noxious input to deep tissues, but it did not provide any genotyping. Longitudinal studies with genotyping of candidate genes are needed as a further step, which should be taken into consideration for future studies.

The present study was not designed to implement immediate changes in prevention or management of patients, but merely to explore the possibility that multiple factors may be involved in the pathophysiology of pain sensitivity. As the study revealed that patients with a deep bite before orthodontic treatment may be more pain sensitive, this finding may have implications for the management of pain during orthodontic treatment of these patients.

Conclusions

The present study provides further evidence of sex-related differences in somatosensory sensitivity and, for the first time, indicates that subjects with a deep bite may be more pain sensitive to deep thermal and chemical noxious stimuli.

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References

1. Forssell H, Kalso E. Application of principles of evidence-based medicine to occlusal treatment for temporomandibular disorders: Are there lessons to be learned? J Orofac Pain 2004;18:9–22.
2. De Boever JA, van den Berghe L. Longitudinal study of functional conditions in the masticatory system in Flemish children. Community Dent Oral Epidemiol 1987;15:100–103.
3. Riolo ML, Brandt D, TenHave TR. Associations between occlusal characteristics and signs and symptoms of TMJ dysfunction in children and young adults. Am J Orthod Dentofac Orthop 1987;92:467–477.
4. Gunn SM, Woolfolk MW, Faja BW. Malocclusion and TMJ symptoms in migrant children. J Craniomandib Disord Facial Oral Pain 1988;2:196–200.
5. Jämsä T, Kirveskari P, Alanen P. Malocclusion and its association with clinical signs of craniomandibular disorder in 5-, 10-, and 15-year old children in Finland. Proc Finn Dent Soc 1988;84:235–240.
6. Keeling SD, McGorray S, Wheeler TT, King GJ. Risk factors associated with temporomandibular joint sounds in children 6 to 12 years of age. Am J Orthod Dentofac 1994;105:279–287.
7. Sonnesen L, Bakke M, Solow B. Malocclusion traits and symptoms and signs of temporomandibular disorders in children with severe malocclusion. Eur J Orthod 1998;20:543–559.
8. Thilander B, Rubio G, Pena L, de Mayorga C. Prevalence of temporomandibular dysfunction and its association with malocclusion in children and adolescents: An epidemiologic study related to specified stages of dental development. Angle Orthod 2002;72:146–154.
9. Vanderas AP, Papagiannoulis L. Multifactorial analysis of the aetiology of craniomandibular dysfunction in children. Int J Paediatr Dent 2002;12:336–346.
10. Egermark I, Magnusson T, Carlsson GE. A 20-year follow-up of signs and symptoms of temporomandibular disorders and malocclusions in subjects with and without orthodontic treatment in childhood. Angle Orthod 2003;73:109–115.
11. Gesch D, Bernhardt O, Kirbschus A. Association of malocclusion and functional occlusion with temporomandibular disorders (TMD) in adults: A systematic review of population-based studies. Quintessence Int 2004;35:211–221.
12. Lieberman MA, Gazit E, Fuchs C, Lilos P. Mandibular dysfunction in 10–18 year old school children as related to morphological malocclusion. J Oral Rehab 1985;12:209–214.
13. Lous I, Jacobsen R, Seidler B. Occurrence of muscle contraction headache in children with abnormal incisor occlusion [in Danish]. Dan Dent J 1989;93:705–709.
14. Kritsineli M, Shim YS. Malocclusion, body posture, and temporomandibular disorder in children with primary and mixed dentition. J Clin Pediatr Dent 1992;16:86–93.
15. Sonnesen L, Svensson P. Temporomandibular disorders and psychological status in adult patients with a deep bite. Eur J Orthod 2008;30:621–629.
16. Cairns BE, Svensson P, Wang K, et al. Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2003;90:2098–2105.
17. Cairns BE, Svensson P, Wang K, et al. Ketamine attenuates glutamate-induced mechanical sensitization of the masseter muscle in human males. Exp Brain Res 2006;169:467–472.

18. Svensson P, Sessle BJ. Orofacial pain. In: Miles TS, Nauntofte B, Svensson P (eds). Clinical Oral Physiology. Copenhagen: Quintessence, 2004:93–139.
19. Bendtsen L, Jensen R. Tension-type headache: The most common, but also the most neglected, headache disorder. Curr Opin Neurol 2006;19:305–309.
20. Ashina S, Bendtsen L, Ashina M. Pathophysiology of tension-type headache. Curr Pain Headache Rep 2005;9: 415–422.
21. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: A population study. Pain 2006;123:19–27.
22. Ballegaard V, Thede-Schmidt-Hansen P, Svensson P, Jensen R. Are headache and temporomandibular disorders related? A blinded study. Cephalalgia 2008;28:832–841.
23. Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341–351.
24. Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pressure-pain thresholds and stimulus-response curves. J Orofac Pain 1995;9:347–356.
25. Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. Pain 1998;76:71–81.
26. Sarlani E, Grace EG, Reynolds MA, Greenspan JD. Evidence for up-regulated central nociceptive processing in patients with masticatory myofascial pain. J Orofac Pain 2004;18:41–55.
27. Sarlani E, Garrett PH, Grace EG, Greenspan JD. Temporal summation of pain characterizes females but not males with temporomandibular disorders. J Orofac Pain 2007;21: 309–317.
28. Raphael KG. Temporal summation of heat pain in temporomandibular disorder patients. J Orofac Pain 2009;23: 54–64.
29. Hollins M, Harper D, Gallagher S, et al. Perceived intensity and unpleasantness of cutaneous and auditory stimuli: An evaluation of the generalized hypervigilance hypothesis. Pain 2009;141:215–221.
30. Castrillon EE, Cairns BE, Ernberg M, et al. Effect of a peripheral NMDA receptor antagonist on glutamate-evoked masseter muscle pain and mechanical sensitization in females. J Orofac Pain 2007;21:216–224.
31. Svensson P, Cairns BE, Wang K, et al. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain 2003;101:221–227.
32. Svensson P, Wang K, Sessle BJ, Arendt-Nielsen L. Association between pain and neuromuscular activity in the human jaw and neck muscles. Pain 2004;109:225–232.
33. Castrillon EE, Cairns BE, Ernberg M, et al. Glutamate-evoked jaw muscle pain as a model of persistent myofacial TMD pain? Arcj Oral Biol 2008;53:666–676.
34. Schmidt-Hansen PT, Svensson P, Bendtsen L, Graven-Nielsen T, Bach FW. Increased muscle pain sensitivity in patients with tension-type headache. Pain 2007;129:113–121.
35. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders: Pathways of vulnerability. Pain 2006;123:226–230.
36. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: A consensus report. Pain 2007;132:S26–S45.
37. Quiton RL, Greenspan JD. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. Pain 2007;132:S134–S149.
38. Slade GD, Diatchenko L, Ohrbach R, Maixner W. Orthodontic treatment, genetic factors and risk of temporomandibular disorder. Semin Orthod 2008;14:146–156.
39. Solow B. Orthodontic screening and third party financing. Eur J Orthod 1995;17:79–83.
40. Melzack R, Katz J, Jeans ME. The role of compensation in chronic pain: Analysis using a new method of scoring the McGill pain questionnaire. Pain 1985;23:101–112.
41. Svensson P, Bak J, Troest T. Spread and referral of experimental pain in different jaw muscles. J Orofac Pain 2003;17:214–223.
42. Cairns BE, Svensson P, Wang K, et al. Ketamine attenuates glutamate-induced mechanical sensitization of the masseter muscle in human males. Exp Brain Res 2006;169:467–472.
43. Svensson P, Baad-Hansen L, Thygesen T, Juhl GI, Jensen TS. Overview on tools and methods to assess neuropathic trigeminal pain. J Orofac Pain 2004;18:332–338.
44. Baad-Hansen L, Jensen TS, Svensson P. A human model of intraoral pain and heat hyperalgesia. J Orofac Pain 2003; 17:333–340.
45. Lim PF, Smith S, Bhalang K, Slade GD, Maixner W. Development of temporomandibular disorders is associated with greater bodily pain experience. Clin J Pain 2010;26: 116–120.