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A COMPARATIVE STUDY OF THE EFFECTIVENESS OF A PREFABRICATED APPLIANCE AND A STABILIZATION APPLIANCE IN THE TREATMENT OF MYOFASCIAL PAIN AND HEADACHE

by

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"Cure sometimes
treat often
comfort always"

Hippocrates

To Linda and Axel

ABSTRACT

Marika Doepel

A Comparative Study of the Effectiveness of a Prefabricated Appliance and a Stabilization Appliance in the Treatment of Myofascial pain and Headache

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The aim of this thesis was to evaluate the short- and long-term effectiveness of a prefabricated occlusal appliance (R) on patients with myofascial pain and headache by comparing it with the treatment of the stabilization appliance (S). Another aim was to evaluate the effect of appliance treatment on stress-related salivary parameters like cortisol and IgA, as well as on flow rate values in these patients.

Sixty-five patients diagnosed with myofascial temporomandibular disorder (TMD) pain, of whom 94% suffered concomitantly from headache, at two centres for Stomatognathic Physiology, one in Sweden and one in Finland, were included in this randomized controlled trial using Research Diagnostic Criteria for TMD (RDC/TMD), with history questionnaires and clinical examinations performed at baseline and at 6- and 10-weeks, and 6- and 12-month follow-ups. Patients were randomly assigned either to the R or the S group. Treatment outcome was measured according to IMMPACT (Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials), i.e. four chronic pain outcome domains: pain intensity, overall improvement, physical and emotional functioning. Changes in frequency and intensity of headache were recorded. Thirty-nine patients participated in the saliva study. Salivary analyses were performed at 6 and 10 weeks.

The results revealed no differences between groups at baseline. At all follow-ups, all four outcome measures, as well as frequency and intensity of headache, showed statistically significant within-group improvement compared to baseline, without significant differences between groups. No treatment-induced changes in saliva parameters could be registered.

In conclusion, the effectiveness of the prefabricated appliance seemed to be similar to that of the stabilization appliance in alleviating myofascial pain, and frequency and intensity of headache, in the short as well as the long term. However, no changes in salivary parameters were observed during treatment.

Key words: headache, long-term follow-up, myofascial pain, occlusal appliances, pain, randomized controlled trial, saliva, salivary cortisol, salivary IgA, stress, temporomandibular disorders, TMD.

TIIVISTELMÄ

Marika Doepel
Esivalmistetun purentakiskon ja stabilisaatiokiskon tehokkuutta vertaava tutkimus purentaelimen toimintahäiriöistä ja päänsärystä kärsivillä potilailla.
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Tutkimus selvitti esivalmistetun relaksaatiotyyppisen purentakiskon (R) tehokkuutta verrattuna perinteiseen stabilisaatiokiskoon (S), sekä lyhyt- että pitkäaikaisseurannassa, kun hoidetaan purentaelimen toimintahäiriöistä johtuvia lihasperäisiä kasvokipuja, sekä jännityspäänsärkyä. Lisäksi tarkoituksena oli arvioida kiskohoidon vaikutusta kivun aiheuttamaan stressiin ja sen heijastumista sylkimuuttujissa, kuten syljen kortisoli ja IgA, sekä syljen eritys.

Tutkimukseen valittiin tarkkojen kriteereiden perusteella kuusikymmentäviisi aikuispotilasta, joilla kaikilla oli diagnosoitu lihasperäiset kasvokivut ja joista 94% kärsi päänsärystä. Tutkimus toteutettiin yhteistyöprojektina Malmön korkeakoulun hammaslääketieteen laitoksen kanssa. Turussa hoidettiin 33 henkilöä ja Malmössa 32 henkilöä, puolet esivalmistetulla kiskolla ja puolet stabilisaatiokiskolla. Potilaat tutkittiin RDC/TMD kriteerien mukaan. Kuuden ja 10 viikon sekä 6 ja12 kuukauden seurannan jälkeen heidät tutkittiin uudestaan. Potilaat valittiin satunnaisesti joko R tai S ryhmään. Tutkimuksen suorittaja oli sokkoutettu ja kiskohoidon toteutti peruskoulutettu hammaslääkäri. Sylkitutkimukseen osallistui 39 potilasta ja sylkianalyysit tehtiin 6 ja 10 viikon kohdalla.

Hoitotulokset arvioitiin käyttämällä IMMPACTia (Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials). Kroonista kipua arvioitaessa käytettiin neljä kriteeriä: kivun intensiteetti, potilaan arviointi kivun lievittymisestä ja fyysinen ja psyykkinen toimintakyky. Lisäksi rekisteröitiin muutokset päänsäryn intensiteetissä ja frekvenssissä .

Ryhmät eivät eronneet toisistaan tutkimuksen alkutilanteessa. Molemmissa ryhmissä havaittiin tilastollisesti merkitsevää paranemista jokaisessa seurantapisteessä kaikkien neljän arviointikriteerin, sekä päänsäryn frekvenssin ja intensiteetin osalta. Ryhmien välillä ei ollut tilastollista eroa. Syljen muuttujissa ei havaittu muutoksia hoidon aikana.

Sekä lyhyt- että pitkäakaisen seurannan perusteella voidaan todeta,että esivalmistettu kisko vaikuttaa olevan tehokkuudeltaan verrattavissa stabilisaatiokiskoon hoidettaessa lihasperäistä kasvokipua ja päänsärkyä.

Avainsanat: kipu, lihsperäinen kipu, pitkäaikais-seuranta, purentaelimistön toimintahäiriöt, purentakisko, päänsärky, sokkoutettu kontrolloitu tutkimus, stressi, sylki, syljen IgA, syljen kortisoli, TMD

SAMMANFATTNING

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Effekten av en prefabricerad skena jämfört med en stabiliseringsskena vid behandling av myofasciell smärta och huvudvärk
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Målet med studien var att utvärdera, både i ett korttids- och i ett långtidsperspektiv, en prefabricerad bettskenas effektivitet i vården av patienter med myofasciell smärta och huvudvärk jämfört med en stabiliseringsskena, samt att utvärdera bettskenebehandlingens effekt på stressrelaterade saliv-parametrar, så som cortisol och IgA, samt salivflödet.

Sextiofem patienter, alla med diagnosen myofasciell smärta, och 94% av dem med huvudvärk, inkluderades i denna randomiserade, kontrollerade studie. Studien utfördes i samarbete med Odontologiska fakulteten vid Malmö Högskola. I Åbo behandlades 33 patienter och i Malmö 32, hälften med den prefabricerade skenan (R) och hälften med en stabiliseringsskena (S). Patienterna randomiserades till grupp R eller grupp S. Patienterna undersöktes enligt RDC/TMD med frågeformulär och kliniska undersökningar före studiens början och vid 6 och 10 veckor, samt 6 och 12 månader. Behandlingsresultatet utvärderades enligt IMMPACT (Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials), med följande fyra kriterier: smärtintensitet, generell förbättring, fysisk och emotionell funktionsduglighet. Förändringar i intensitet och frekvens av huvudvärk registrerades. Trettionio patienter deltog i salivstudien. Salivproven analyserades vid 6 och 10 veckor.

Ingen skillnad mellan grupperna kunde noteras vid studiens början. Under uppföljningen hade alla fyra utvärderingskriterier sjunkit statistiskt signifikant vid varje uppföljningstidpunkt, utan statistisk skillnad mellan grupperna. Även frekvensen och intensiteten på huvudvärken sjönk statistiskt signifikant vid varje uppföljning, utan statistisk skillnad mellan grupperna. Det kunde inte påvisas att bettskenebehandlingen skulle ha haft någon effekt på salivparametrarna.

Den prefabricerade skenan verkar ha lika god effektivitet vid behandlingen av myofasciell smärta, och åtföljande huvudvärk, som stabiliseringsskenan, både i ett korttids- och ett långtidsperspektiv. Inga förändringar i salivfaktorerna kan konstateras under vårdens gång.

Nyckelord: bettskena, huvudvärk, långtids-uppföljning, myofasciell smärta, randomiserad kontrollerad studie, saliv, salivens cortisol, salivens IgA, smärta, stress, temporomandibulär dysfunktion, TMD

CONTENTS

ABBREVIATIONS

The following abbreviations appear in the text:

CBT	cognitive-behavioural therapy
CD	craniomandibular disorders
COMT	catechol-O-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials
CPI	characteristic pain intensity
CT	computerized tomography
EACD	European Academy of Craniomandibular Disorders
GCP	graded chronic pain
HPA	hypothalamic-pituitary-adrenal
ICHD	International Classification for Headache Disorders
IgA	immunoglobulin A
IMMPACT	Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials
JFLS-20	Jaw Functional Limitation Scale 20-Item Version
MRI	magnetic resonance imaging
NNT	number needed to treat
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NSPhS	nonspecific physical symptoms
NTI	Nociceptive Trigeminal Inhibition Tension Suppression System
PPT	pressure pain threshold
RCT	randomized controlled trial
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
SCL-90-R	Symptom Check List-90-Revised
TENS	transcutaneous electric nerve stimulation
TMD	temporomandibular disorders
TMJ	temporomandibular joint
TTH	tension type headache
UT	usual conservative treatment
VAS	visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I to IV

I Nilner M, Ekberg EC, Doepel M, Andersson J, Selovuo K, Le Bell Y. Short-term Effectiveness of a Prefabricated Occlusal Appliance in Patients with Myofascial Pain. *J Orofac Pain 2008;*22:209-218.

II Doepel M, Söderling E, Ekberg EC, Nilner M, Le Bell Y. Salivary cortisol and IgA levels in patients with myofascial pain treated with occlusal appliances in the short term. *J Oral Rehabil 2009;*36:210-216.

III Doepel M, Nilner M, Ekberg EC, Le Bell Y. Long-term Effectiveness of a Prefabricated Oral Appliance for Myofascial Pain. *Manuscript*

IV Doepel M, Nilner M, Ekberg EC, Vahlberg T, Le Bell Y. Headache – short- and long-term effectiveness of a prefabricated appliance compared to a stabilization appliance. *Acta Odontol Scand 2011;* 69:129-136.

1. INTRODUCTION

Musculoskeletal pain involving the masticatory muscles and pain of the temporomandibular joints (TMJ) and adjacent tissues (Laskin et al. 2006) is one of the most prevalent orofacial pain conditions. It is associated with impaired function of the jaws, quality of life, sick leave, and increased use of health care (Kuttila et al. 1997b, White et al. 2001). Since 1934, signs and symptoms of musculoskeletal disorders in the jaw/face have been given various names, like Costen`s syndrome, TMJ pain-dysfunction syndrome, functional TMJ disturbances, myofacial pain-dysfunction syndrome, craniomandibular disorders (CD), mandibular dysfunction, and internal derangements of TMJ. Since 1991 (McNeill 1993), temporomandibular disorders (TMD) has been the best established and most often used term.

In adults, signs and symptoms of TMD occur frequently , more often in women than in men (LeResche 1997, Kuttila et al. 1997a, Carlsson 1999). Patients suffering from TMD often present with pain in the jaws, earache, headache, and myofascial pain. The pain is often aggravated by mandibular movements, like chewing and yawning. It is also frequently associated with disturbed function and limited and/or assymetric movements of the lower jaw (Okeson (ed) 1996, Schindler and Svensson 2007).

The etiology of TMD is complex and not clearly known, but, in general, it is believed to be multifactorial (McNeill 1993) including anatomical factors, such as occlusal factors, general health and psychological factors (Schindler and Svensson 2007). Biopsychosocial aspects have been mentioned in several studies (Dworkin & LeResche 1992, Dworkin 1997, Suvinen et al. 2005). Recently, neuroendocrine and genetic factors, as well as peripheral and central mechanisms, have been focused on (Svensson et al. 2003, Zubieta et al. 2003).

General management aims at relief of pain and restoration of jaw mobility and impaired chewing function, and includes several options such as occlusal appliances, pharmacotherapy, physical self-treatment, physical therapy, acupuncture, and behavioural management (Schindler & Svensson 2007). Several studies have shown good treatment results for occlusal appliance therapy, although the actual working mechanism of occlusal appliances is not known (Ekberg et al. 1998, 2003, Raphael & Marbach 2001, Ekberg & Nilner 2002, 2004). However, more randomized controlled studies (RCTs) have been called for (Forssell et al. 1999, Forssell & Kalso 2004).

2. REVIEW OF THE LITERATURE

2.1. Temporomandibular Disorders

2.1.1. Epidemiology and prevalence

Epidemiologic research has demonstrated a high prevalence of signs and symptoms of TMD in virtually all examined populations and age groups (Carlsson 1999, LeResche 2001). A meta-analysis of 51 TMD studies showed a prevalence of 30% (6-93%) for reported symptoms, and 44% (0-93%) for clinical signs (DeKanter et al. 1993). According to Nilner (1992), the registration of subclinical signs and the fluctuation of signs and symptoms are two reasons for the high prevalence presented. In a recent study (Johansson et al. 2008), it was concluded that the prevalence of TMD remained relatively consistent during a 10-year follow-up; those reporting symptoms at the first examination were highly likely to still have them 10 years later. On the other hand, with regard to the differences in reported percentages, it has to be noted that epidemiological findings will obviously depend on assessment strategies: some investigators only look at palpation findings, while others rely on patient reports. In a summary of 17 epidemiological studies, 41 % reported at least one symptom associated with TMD, and 56% showed at least one clinical sign (Okeson 2008). In a German population-based study (Gesch et al. 2004), 10% reported TMJ symptoms, and 50% had one or more clinical signs of TMD. Pain in the temporomandibular region occurs in about 10% of the adult population (LeResche 1997). The prevalence in children is slightly lower, and the symptoms are usually milder than in adults (List et al. 1999, Liljeström et al. 2001, Magnusson et al. 2005). The prevalence increases, however, with pubertal onset (LeResche et al. 2005).

Both symptoms and signs of TMD are often mild, and TMD does not necessarily always need any treatment. There is considered to be a need for treatment in 3-11% of patients (DeKanter et al. 1993, Kuttila et al. 1998, Magnusson et al. 2005). The prevalence figures cannot be directly transformed into estimations of TMD treatment need. To separate prevalence figures from treatment need figures, the concept of dividing patients into groups of active, passive, and no treatment need for TMD was introduced (Kuttila et al. 1997a). Active treatment need figures varied from 7% to 9% (Kuttila et al. 1997a), and were almost the same as in some cross-sectional studies (Schiffman et al. 1990, De Kanter et al. 1993), but clearly lower than in some early epidemiological studies (Helkimo 1974, Agerberg and Inkapööl 1990, Magnusson et al. 1991, 1994). In a recent meta-analysis, however, the treatment need was estimated at 16% (Al-Jundi et al. 2008). The prevalence figure of treatment need itself indicates that TMD is a significant health problem. A fluctuating pattern over the years seems to be common to both symptoms and signs (Könönen et al. 1993, Magnusson et al. 2005), but symptoms seldom progress to severe pain and dysfunction.

2.1.2. Gender and age

There is a strong female predominance among patients in TMD clinics. A higher prevalence of most TMD signs and symptoms has been found in women than in men (Wänman 1996,

LeResche 1997, Carlsson 1999, Egermark et al. 2001). Women, especially those between 30 and 39 years, are up to four times more frequently affected than males (Kuttila et al.1998, List et al. 1999). Women had nearly twice the rate of jaw joint pain than men, and more than twice the rate of face pain (Dao and LeResche 2000). In a review of six population-based studies from five countries (LeResche 2001), it was calculated that pain in the temporomandibular region was experienced by 11.3% of women and 6.5% of men. A Swedish study (Johansson et al. 2003) came to much the same conclusion in a population study consisting of 8888 adults; pain in the TMJ had a prevalence of 12.7% in women, and 6.7% in men. Women are also less likely to recover from their symptoms (Wänman 1996), and are more likely to seek treatment (Carlsson 1999).

It has been suggested that the higher prevalence of chronic orofacial pain found in women is a result of sex differences in generic pain mechanisms and of yet unidentified factors unique to the craniofacial system (Dao and LeResche 2000). Genetic variants of the enzyme catechol-O-methyltransferase (COMT) activity have been associated with enhanced experimental pain sensitivity and amplified risk of developing TMD (Zubieta et al. 2003, Diatchenko et al. 2005). Thus, pain genetics might partly explain the individual vulnerability to pain perception. There are indications that endogenous or exogenous hormones, such as the estrogens, and their influence on nerve growth factor and nociception, may play a role in the genesis of TMD pain. Intramuscular injection of 5-HT was perceived as more painful in women than in men (Ernberg et al. 2000). Recent studies have shown that injections of nerve growth factor into the masseter muscle cause long-lasting muscle allodynia and pain associated with strenuous jaw movements, which seems to be more pronounced in women than in men (Svensson et al. 2003). In another recent study, basal pressure pain threshold (PPT) values were found to be lower in healthy muscles of women than in men (Christidis et al. 2005). These findings may offer an explanation for the well-known clinical observation that women, especially during childbearing age, are more often affected by pain in the area of the jaw musculature then men.

TMD occurs already in childhood (Magnusson et al. 2005, Nilsson et al. 2005), and seems to increase with age and show a fluctuating pattern (Könönen and Nyström 1993, Wänman 1996, Liljeström et al. 2001, Magnusson et al. 2005). The peak is reached between 20 and 40 years of age (Okeson 2008), between the age of 50 and 60 it seems to remain quite constant (Johansson et al. 2008), and after retirement the prevalence gradually decreases (Österberg et al. 1992). The reason for the decrease is not known, but one explanation has recently been offered: as the number of missing posterior teeth increases with increasing age, the possibility of occlusal interferences decreases (Wang et al. 2009).

2.1.3. Etiology and risk factors of TMD

The etiology of TMD is usually considered multifactorial. In general, no specific event, condition or characteristic is by itself sufficient to produce the disease, but a causal complex with many factors is needed (Rothman and Greenland, 1998).

A common model in the numerous mechanisms considered as potential risk sources of myofascial TMD pain, involves nociceptor pain, which is triggered by strain in the musculature, such as micro trauma caused by repeated overloading of the jaw system (Okeson 1996), overloading in relation to the tissues´ capacity to adapt to or restrain to load (Wänman and Agerberg 1991, Stegenga and de Bont 2006), joint hyper-mobility (Hirsch et al. 2008), external trauma (Pullinger and Seligman 1991), or impaired jaw function following, e.g. a whiplash trauma (Eriksson et al. 2007, Grönqvist et al. 2008, Severinsson et al. 2010). Variations in the occlusion (Mohlin et al. 1984, Sipilä et al. 2002, Pullinger and Seligman 2000, Marklund and Wänman 2010), deep bite and a small mandible (Pahkala et al. 2002), bruxism (Huang et al. 2002, Velly et al. 2003, Magnusson et al. 2005,), severe wear of teeth, and joint clicking (Carlsson et al. 2004, Seligman and Pullinger 2006, Marklund and Wänman 2010), as well as anterior occlusal wear in relation to age (Seligman and Pullinger, 2000, 2006, Carlsson et al. 2002) have been considered to be possible risk factors for the development of TMD. Loss of posterior tooth support may be a contributing factor for TMJ pain (Ciancanglini et al. 1999, 2003, Sarita et al. 2003, Seedorf et al. 2004, Wang et al. 2009). Occlusal interferences (Kirveskari et al. 1989, 1998, Le Bell et al. 2002), and especially a long slide from the retruded position to the intercuspal position (Pullinger and Seligman 2000, Pahkala and Laine-Alava 2002) are considered risk factors for TMD. In a recent study, it was concluded that mandibular instability in centric positions predicted onset and persistence of TMJ pain and dysfunction (Marklund and Wänman 2010). Elimination of occlusal interferences was reported to reduce the incidence of TMD in subjects who underwent occlusal adjustment, in comparison to mock adjustment (Kirveskari et al. 1989a, 1989b, 1998). Subjects with an earlier history of TMD were found to be more vulnerable to changes in the dental occlusion (Le Bell et al. 2002, 2006). However, the influence of occlusal factors with regard to the occurrence and prolongation of myofascial TMD pain may play a lesser role than has been traditionally assumed (Gesch et al. 2004, Schindler and Svensson 2007).

Recent studies have consistently confirmed that self-reported bruxism, as well as other parafunctions, are possible risk factors for TMD (Huang et al. 2002, Velly et al. 2003, Magnusson et al.2005). However, the role of bruxism as an initiating risk factor in TMD has been questioned (Barbosa et al. 2008), and the scientific evidence of its influence on TMD (DeBoever and Carlsson 1994, Lobbezoo and Lavigne 1997), and craniofacial pain (Svensson et al. 2008) has been considered weak.

There seems to be widespread agreement that stress, depression, disability and dysfunctional illness behaviours are critical aspects of the TMD patient´s profile (Dworkin and LeResche 1992, Dworkin 1997). TMDs are associated with the same significant psychological and psychosocial issues, as well as behavioural factors, that are found in all chronic pain conditions, orofacial or otherwise (Von Korff et al. 1988a, 1988b, Dworkin and LeResche 1992, Turner et al. 2001, Manfredini et al. 2003, Rollman and Gillespie 2004). Psychological factors and depression (Niemi et al. 2006, Slade et al. 2007), as well as social and general health factors (Johansson et al. 2004), have been regarded as risk or contributing factors. On the other hand, pain as such causes

discomfort, stress, and stress reactions. There is no clear evidence of whether the reported increased stress level in patients with TMD-related pain is the cause or effect of TMD and TMD-related pain (Turner et al.1995, Manfredini et al. 2004). Among others, Niemi and co-workers (1993) reported TMD patients to have more stress symptoms than healthy controls. A decrease in stress-related and emotional reactions after treatment, when compared with non-treated TMD controls, has been shown (De Leeuw et al 1994). Questionnaire-derived psychological measurements have shown more distress in patients with muscular symptoms compared with those with internal derangements (Eversole et al. 1985) or joint pain (McCreary et al. 1991). More dysfunctional profiles have also been found among muscle-pain patients compared with intracapsular-pain patients (Lindroth et al. 2002). Others have found that the location of pain was not a major factor in the prediction of psychosocial profiles (Reissman et al. 2008).

2.2. Headache and TMD

Headache, especially tension-type headache (TTH), has been reported as a complaint in about 40-70% of patients suffering from TMD (Magnusson and Carlsson 1978a, Pettengrill 1999), and there is evidence that the prevalence of headaches is high in patients with myofascial TMD pain (70%) (Okeson 1996). Conversely, 50% of headache patients show symptoms of myofascial TMD pain (Shokker et al. 1990b). Many studies have shown an association between headache and TMD (Magnusson and Carlsson 1978a, 1983, Forssell et al. 1985, Shokker et al. 1990a, Vallon et al. 1998, Glaros et al. 2007, Ballegaard et al. 2008). On the other hand, although TMD and headache frequently occur together, it could be simply by chance, because both disorders are extremely prevalent (Rasmussen et al. 1991, De Kanter et al. 1993, Jensen et al. 1993b).

Of the variables included in the guidelines for the evaluation, diagnosis, and management of TMD (Dworkin and LeResche 1992, McNeill 1993), only masticatory muscles painful to palpation has been consistently found to have a clear relationship to headache (Gelb and Tarte 1975, Magnusson and Carlsson 1978b, Headache Classification Committee of the International Headache Society 1988). A highly significant positive association between frequency of TTH and tenderness in pericranial muscles, independent of TMD, has been reported (Jensen et al. 1993a). Frequency and severity of headache have been found to vary with the severity of the tenderness in pericranial muscles (Magnusson and Carlsson 1978b, 1980, Wänman and Agerberg 1986, Jensen et al. 1993a, 1993b), but no other significant correlation has been found between headache and TMD signs and symptoms.

Tension-type headaches can be frequent and severe, and cause great invalidity to those suffering from them (Rasmussen et al.1991). In a Danish population study (Rasmussen et al. 1992), only 16% of patients with TTH had contacted a general practitioner because of headache compared to 56% of migraineurs, but when the data were corrected for the markedly higher prevalence of TTH, the total use of medical services was in fact 54% higher for TTH . This supports the fact that TTH is one of the most costly diseases, causing roughly three times more sick leaves than migraine.

The exact relationship between TMD and headache is largely unknown. In a recently published study (Ballegaard et al. 2008), the authors indicated that a high proportion of headache patients have significant disability because of ongoing chronic TMD pain, and they emphasized the importance of examining the masticatory system in headache sufferers.

It has been shown that treatment of TMD with occlusal appliances or occlusal adjustment reduced overall headache, TTH, or combination headache (Forssell et al. 1985 , Vallon et al. 1991, 1995, Karppinen et al. 1999, Ekberg et al. 2002, Ekberg and Nilner 2006). The stabilization appliance seems to have a positive effect on the frequency of TTH in patients with TMD pain of both arthrogenous and myogenous origin (Vallon et al.1995, 1998, Ekberg et al.2002, Ekberg and Nilner 2006), both in the short and the long term.

2.3. Salivary parameters

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been linked to stress in patients with TMD (Evaskus and Laskin 1972). In this context, cortisol has gained much attention as a "stress hormone". It has been shown that salivary cortisol is a valid indicator of cortisol concentration in serum (Saliva Diagnostics 2006, Vining and McGinley 1987). Salivary cortisol secretion has a diurnal rhythm with a peak in the morning, around one hour after waking (Saliva Diagnostics 2006).

Psychological stress, for example, affects salivary cortisol levels (Kirschbaum and Hellhammer 1994), although individual reactions may vary. In a stressful situation, when exposed to a standardized test, some students, "high responders", revealed high cortisol levels, while others, "low responders", showed no such increase (Kirschbaum et al. 1995).

The cortisol level has been found to be significantly higher in patients with TMD, compared to healthy controls, during the daytime (Korszun et al. 2002). In a recent study, TMD patients could be divided into two groups, one that hypersecreted cortisol in response to stress, while the other was no different from the control group (Jones et al. 1997). Depression scores and salivary cortisol levels on waking were found to be significantly higher in women with signs and symptoms of TMD, than in men or controls (Da Silva Andrade et al. 2008). However, in another study (Galli et al. 2009), the levels were similar to those in matched controls.

Immunoglobulin A or IgA is the major immunoglobulin in the fluids on the mucosal surfaces where especially secretory IgA plays an important role in the defence mechanisms of the human body. Secretory IgA can easily be determined from saliva and is affected by saliva flow rate (Valdimarsdottir and Stone 1997). Several studies have examined the relation between IgA and stressful circumstances, ranging from major life events to daily hassles, but the results have been contradictory (Valdimarsdottir and Stone 1997).

It may also be possible that stress induces changes in the masseter muscle (Hidaka et al. 2004) and, thereby, the function of the parotid gland and the secretion of saliva might be

affected. In a study on unmedicated TMD patients, an increase in flow rate values was observed after successful treatment (Le Bell et al. 1985).

2.4. Diagnostics of TMD

As no scientifically confirmed all-embracing hypothesis exists regarding the etiology of myofascial TMD pain, the diagnostic process relies on case history, i.e. the description of symptoms, and clinical examination, and should be based on the following procedures:

(1) the symptoms reported by the patient,

(2) the clinical examination, preferably according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin and LeResche 1992),

(3) and on special indications imaging

The RDC/TMD (Dworkin and LeResche 1992), Table 1, was created to provide a classification system that allows for standardization and replication of research focusing on jaw muscle- and TMJ-related pain and dysfunction. The RDC/TMD uses a dual-axis classification system that allows a physical diagnosis placed on Axis I, and an assessment of TMD-related behavioural limitations, psychological distress, and psychosocial dysfunction, increasingly important when chronicity plays a more prominent role, on Axis II. The importance of calibration of clinicians using the RDC/TMD has been emphasized by the authors (Dworkin et al.1990), and a recommended pre-training study site protocol has been set up for the use of RDC/TMD (www.rdc-tmdinternational.org). The RDC/TMD has been validated in 20 languages. Dworkin and LeResche, from the beginning, initiated a continuous revision of the RDC/TMD and diagnostic criteria, and an updated diagnostic system has recently been published (Andersson et al. 2010, Look et al. 2010, Ohrbach et al. 2010, Schiffman et al. 2010a, Schiffman et al. 2010b, Truelove et al. 2010).

The diagnoses of the RDC/TMD are assigned on the basis of physical examination and case history in three major Axis I groups: (1) muscle disorders, (2) disc displacements, and (3) arthralgia/arthritis/arthrosis. The diagnostic system is nonhierarchical and allows for the possibility of multiple diagnoses for a subject. Thus, a subject can be assigned a muscle diagnosis and one diagnosis from group 2 and group 3 for each joint. Muscle disorders are divided into two subgroups: (a) myofascial pain, and (b) myofascial pain with limited opening. These diagnoses include a complaint of pain and pain reported in response to palpation of three or more of 20 muscle sites. Most TMD pains are rather episodic in nature and can be easily managed. However, there are patients whose pain persists over a long period despite therapeutic interventions. Such pain may lead to substantial stress and associated psychosocial reactions. The patients´ Axis II profile contains a graded chronic pain status, scores of depression and nonspecific physical symptoms, and a summary score for limitations in the ability to use the jaw. Studies on reliability and validity have been conducted and have shown good results (Dworkin et al. 2002, John et al. 2005). However, the system has also been criticized with regard to, e.g. the diagnosis of an anterior disc

displacement with reduction (Naeije et al. 2009), and for difficulties in confirming TMD pain during the examination procedure (Visscher et al. 2009).

Table 1. Research Diagnostic Criteria for Temporomandibular Disorders - RDC/TMD

Axis I			**Axis II**
Clinical TMD conditions			Pain-related Disability and Psychological Status
Case history Physical examination Radiologic examination			Case history
Diagnosis			Assessment and classification of global severity of the pain condition in terms of:
1. Muscle disorders	2. Disc Displacement	3. Arthralgia/arthritis/ arthrosis	1. Pain Intensity (graded chronic pain, GCP)
a. myofascial pain (report of pain plus pain on palpation of three or more of 20 muscles)	a. with reduction (reciprocal clicking)	a. arthralgia (pain and tenderness in joint)	2. Depression (depression subscales from Symptom Check List-90, SCL-90) Nonspecific Physical Symptoms (Somatization subscales from Symptom Check-list-90, SCL-90)
b. myofascial pain with limited mouth opening	b. without reduction, with limited mouth opening	b. osteoarthritis of TMJ (inflammatory condition)	3. Pain-related Disability (the Jaw Functional Limitation Scale; 20-item Version)
	c. without reduction, without limited mouth opening	c. osteoarthrosis of TMJ (degenerative disorder)	

According to the recommendations by the European Academy of Craniomandibular Disorders (EACD) (De Boever et al. 2008), diagnostics should include a panoramic radiograph complemented with peri-apical radiographs and/or bite wings. Additional imaging techniques, such as computerized tomography (CT) and/or magnetic resonance imaging (MRI) are indicated if fractures, tumours and other hard or soft tissue lesions are suspected (De Boever et al. 2008).

2.5. Management of TMD

Management of TMD aims at relief of pain, reduction of load on masticatory muscles and TMJ, and restoration of normal function. Fast pain relief should be sought to avoid central nervous alterations in the nociceptive system and to improve the chances of therapeutic success (Palla 2002). Several different therapies, most of them conservative and reversible, others irreversible, have been advocated for patients with TMD. A number of successful treatment outcomes have been reported. Therapies may include occlusal appliances, pharmacological interventions, physical therapy, physical self-treatment, psychological intervention, acupuncture, and biofeedback (Schindler and Svensson 2007). More complex

TMD conditions are recommended to be managed using combinations of single therapies (Vallon et al. 1998, Schiffman and Gross 2001, De Boever et al. 2008).

In modern pain control concepts, although these are not yet well documented, it is advised to prevent pain from becoming chronic also by prescribing pain medication in the early stages (List et al. 2003). However, only few controlled studies have been published on the efficacy of different types of drugs in TMD management (Sommer 2002). Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used since the 1970s in treating pain. The good treatment effect of NSAIDs in other musculoskeletal disorders is well documented (Van Tulder et al. 2000). Therefore, despite lacking good RCTs, NSAIDs are often used for alleviating pain in acute TMD pain situations. The effect of muscle relaxants and tranquillizers seems to be only moderate, and the scientific evidence for their effect is sparse (Sommer 2002). In chronic TMD pain conditions, tricyclic antidepressants seem to provide an effective pharmacological treatment for jaw muscle pain (Rizzatti-Barbosa et al. 2003), although good RCTs are lacking. The diagnosis and severity of pain should always determine the use of these medications (Sommer 2002).

The aim of physiotherapy is to ease the patient´s pain, reverse the dysfunction, to restore optimal muscle and joint function, posture, and activities of daily living, and to prevent recurrent episodes. Generally, patients with neck and back pain get better relief from active professionally-coached training, compared to patients who only get general advice about training (Ylinen et al. 2007). The scientific evidence for the effect of massage as a pain-decreasing therapy is insufficient for drawing any conclusions. A combination of active physical training, massage and heat has given a better outcome than merely advice and counselling (Wahlund et al. 2003). There are no RCTs available to confirm the efficacy of physical therapy alone for myofascial TMD pain (Schindler and Svensson 2007), but studies have shown that physiotherapy can be as effective as other therapies (Michelotti et al. 2004, McNeely et al. 2006, Medlicott and Harris 2006). About 50% relief of myofascial TMD pain has been obtained in 4-6 weeks of physiotherapy (De Laat et al.2003). The efficacy of transcutaneous electric nerve stimulation (TENS) is inconclusive (Sluka and Walsh 2003). Physical self-treatment combined with education and counselling to direct the patient to various self-management strategies, including biomedical and behavioural elements (Michelotti et al. 2004, 2005), seems to be as effective as occlusal appliances (Carlson et al. 2001). Less extensive strategies do not show significant therapeutic effects (Wright et al. 1995).

During recent years, attention has focused on psychological interventions, i.e. patient education and counselling and behavioural management, such as cognitive-behavioural therapy (CBT) and biofeedback (Schindler and Svensson 2007). Education and counselling may effectively reduce pain (Michelotti et al. 2004). Behavioural, cognitive behavioural, and psychological therapy are recommended as part of the total treatment because of the role of psychosocial factors (Axis II) in the multifactorial etiology of TMDs (Dworkin et al. 2002, Turner et al. 2006). Habit-reversal techniques using biofeedback proved efficient in decreasing the general tension of the patient (Crider and Glaros 1999).

Some evidence is available suggesting that acupuncture may be as effective as occlusal appliances and placebo acupuncture in treating myofascial TMD pain (Johansson et al. 1991, List and Helkimo 1992, Ernst and White 1999, Goddard et al. 2002).

There are some treatment modalities, such as occlusal therapy, prosthetic reconstructions, orthodontic therapy, and surgical interventions, that may be indicated in selected patients. However, it is important to emphasize that these modalities lead to irreversible changes in some parts of the stomatognathic system. After reduction of pain, occlusal interferences may be removed to provide the patient with occlusal stability between the jaws (De Boever et al. 2008). However, recent literature reviews do not support the use of systematic occlusal adjustment (Forssell et al. 1999, Forssell and Kalso 2004, Koh and Robinson 2003, 2004). Prosthetic therapy in TMD patients is not appropriate for initial TMD treatment and should only be carried out on prosthodontic indication after reversible treatment has alleviated pain and dysfunction (De Boever et al. 2000a & b) If prosthetic treatment is considered in TMD patients, it should be kept as simple and as minimally invasive as possible (Plesh and Stohler 1992, Türp and Strub 1996). Regarding orthodontics, a restricted approach is emphasized: patients should not be treated orthodontically in order to prevent or treat TMDs (Mohlin and Kurol 2003). On the other hand, it has been concluded that patients who have undergone orthodontic treatment are not at a higher risk of developing TMD (Kim et al. 2002, Egermark et al. 2003).

Therapeutic modalities for children and adolescents reported in the literature are information, relaxation therapy, and occlusal appliances (Wahlund et al, 2003), all of which have shown acceptable results. When all teeth, except for the third molar, are fully erupted at the age of 13, a stabilization appliance can be recommended as a part of the management (De Boever et al. 2008).

The majority of myofascial TMD pain patients have a good prognosis, and they respond favourably to therapeutic interventions, so noninvasive, reversible management strategies should always be given priority over invasive, irreversible approaches (Schindler and Svensson 2007).

2.6. Occlusal appliances

The most commonly used treatment modality within dentistry for treating TMD patients is the occlusal appliance. In general, occlusal appliances are regarded as appropriate and helpful for managing temporomandibular joint disorders. Recently two meta-analyses were performed by Fricton and co-workers (2010), one based on seven and the other on three studies out of 44 RCTs assessing the efficacy of intraoral appliances to reduce pain in patients with TMD of both a myogenous and an arthrogenous origin. The authors concluded that hard stabilization appliances, when properly adjusted, show good evidence of modest efficacy in the treatment of TMD pain affecting both muscles and joints, compared to non-occluding appliances and no treatment. They also concluded that other types of appliances have some RCT evidence of efficacy in reducing TMD

pain. However, the potential for adverse events is higher with these appliances and a need for close monitoring in their use is suggested. Previously published systematic reviews including RCTs, however, display somewhat diverging conclusions on the efficacy of occlusal appliance therapy. Kreiner and co-workers (2001) concluded in their review of placebo-controlled studies, randomized wait-list controlled studies, and random-assignment treatment-comparison studies, that occlusal appliances work as behavioural interventions and not as medical devices that produce effects via physical changes in the position of the mandible. On the other hand, they concluded that there is sufficient evidence to support the use of occlusal appliances in the management of localized myalgia or arthralgia of the masticatory system.

Forssell and co-workers (1999) and Forssell and Kalso (2004) concluded in their reviews on the basis of their analysis, that RCTs seem to suggest that the use of occlusal splints may be of some benefit in the treatment of TMD, but the evidence is scarce. Therefore, they called for more well-designed studies. However, these authors made no distinction between TMD diagnosis and subdiagnosis, and types of splints used, which makes the comparison between studies somewhat difficult.

Al-Ani and co-workers (2004) reviewed twelve RCTs where a stabilization splint was compared to acupuncture, bite plates, biofeedback/stress management, visual feedback, relaxation, jaw exercises, non-occluding appliances and minimal/no treatment. The authors found no evidence of a statistically significant difference in the efficacy of stabilization splint therapy in reducing symptoms in myofascial patients with pain compared with other active treatment methods.

There are, however, some RCT studies that clearly show a better treatment outcome with a stabilization appliance compared to a control appliance that covers only the palate, both in the short term and in the long term (Ekberg et al. 1998, 2003, Ekberg and Nilner 2002, 2004).

According to a recent review by Türp and co-workers (2004), most myofascial TMD pain patients may benefit from the incorporation of a stabilization appliance. It has to be emphasized that of these reviews, only Türp made a distinction between specific TMD diagnosis, and focused on the most common clinical scenario in the management of TMD: the management of a patient suffering from pain in the masticatory muscles with an occlusal appliance.

2.6.1. Stabilization appliance

The stabilization appliance is the most common type of occlusal appliance, and also the most extensively studied. In a German questionnaire survey, the stabilization appliance was by far the most frequently used appliance type among general dentists and dental specialists (Ommerborn et al. 2009). It has a smooth, flat surface, with supporting teeth in contact, and is adjusted in the centric relation. The appliance has a canine-protected articulation or group contacts of frontal teeth to avoid mediotrusion-interferences during laterotrusion. At protrusion, it has bilateral, symmetric contacts between canines. It is

also known, with some modifications, as the Tanner appliance, the Fox appliance, the Michigan splint, or the centric relation appliance (Ramfjord and Ash 1994). It has been in use since the 1960s, was introduced by Ramfjord and Ash, and is considered the "gold standard" of all oral appliances (De Boever et al. 2008). It has been recommended by many clinicians around the world for the management of patients with TMDs, including masticatory muscle pain. Therefore, the small number of RCTs studying the stabilization appliance in the treatment of patients with myofascial pain, can be considered surprising.

A clinical trial by Dao and co-workers (1994), Table 2, evaluated the efficacy of oral splints using three experimental groups: a) a passive control, wearing an occlusal splint for 30 min at every visit; b) an active control, wearing a palatal splint 24h/day; and c) a treatment group, wearing an occlusal splint 24h/day. The patients included in the study had a primary diagnosis of myofascial TMD pain and were recruited through media advertisement. Most patients in all groups reported that their condition improved during the 10 weeks trial, and the reduction in the intensity and unpleasantness of myofascial TMD pain was progressive. The authors concluded that oral splints should be regarded as an adjunct to pain patient management rather than as a definitive treatment.

An investigation by Raphael and Marbach (2001), Table 2, in which subjects with widespread pain were excluded in one analysis, indicated that uncomplicated TMD patients with regional myofascial TMD pain may respond favourably and in a specific way to splint therapy. Patients in the study were randomly assigned to treatment with an occluding or a non-occluding palatal hard acrylic splint. After six weeks of treatment, the active splint therapy significantly reduced reports of the worst pain in patients with local pain, but not in patients with widespread pain, compared to those treated with the non-occluding splint. The trend was the same for average pain.

In a short-term study by Ekberg and co-workers (2003), Table 2, patients referred for treatment of TMD , and with a diagnosis of myofascial TMD pain with or without limited opening, were randomly allocated to one of two groups: a treatment group treated with a stabilization appliance and a control group treated with a control, non-occluding appliance. Positive treatment outcomes were found in both groups for both signs and symptoms, and there was a statistically significant difference between the groups in favour of the stabilization appliance. The authors concluded that the stabilization appliance can be recommended for the therapy of this type of patient. The results could be verified in a follow-up long-term study on the same patients (Ekberg and Nilner 2004). If patients reporting a better to symptom-free outcome are considered, the number needed to treat (NNT) in the study by Ekberg and co-workers (2003) is 2.3 (Nilner 2004), which is well in accordance with the pain relief seen in drug studies (Sommer 2002).

In a RCT by Truelove and co-workers (2006), Table 2, 200 patients, diagnosed with TMD were randomly assigned to one of three groups: usual conservative treatment, including jaw relaxation, reduction of parafunctions, thermal packs, NSAIDs, passive opening stretches and suggestions about stress reduction (UT); UT plus an occluding

Table 2. RCTs on patients suffering from mainly myogenous pain treated with a stabilization appliance

	Patients	Treatment intervention	Study duration	Outcome measures	Results
Dao et al. Pain 1994	Female/male patients a) recruited through advertisiments published in local journals or b) referred by dentists to a research clinic n=63	1. Stabilization appliance (24h/day) 2. Stabilization appliance (30 min at each appointment) 3. Non-occluding palatal appliance (24 h/day)	2 weeks baseline + 8 weeks treatment	- pain intensity and unpleasentness at rest and after experimental mastication - effect of pain on quality of life	- statistically significant improvement within groups, but not between groups
Raphael & Marbach J Am Dent Assoc 2001	Female patients attending an orofacial treatment centre and referred by dentists n=63	1. Maxillary occluding flat plane splint covering the palate (during night) 2. Maxillary non-occluding flat plane splint partly covering the palate (during night)	6 weeks	- pain on palpation - self-reported pain - functional outcome	- statistically significant decrease of worst pain in patients with local pain treated with an active splint - statistically significant decrease in least pain in the active splint group as compared to the control group
Ekberg et al. J Orofac Pain 2003	Female/male patients referred for (and requesting) TMD treatment n=60	1. Maxillary stabilization appliance (during night) 2. Non-occluding palatal appliance (during night)	10 weeks	- improvement of overall subjective symptoms - intensity and frequency of myofascial pain - pain on palpation - pain at rest / movement	- statistically significant improvement of symptoms in both groups and of signs in appliance group - statistically significant decrease of both signs and symptoms in appliance group as compared to the control group
Truelove et al. J Am Dent Assoc 2006	Female/male patients referred for TMD treatment n=200	1. Usual selfcare treatment, UT 2. UT plus flat-plane splint (2h/day+during night) 3. UT plus soft vinyl splint (2h/day+during night)	12 months	- CPI-mean of present, average and worst TMD-related pain in the past two months - additionally: - self-reported clenching, bruxism - limitation of jaw use - clinical findings & diagnoses - pain duration	- statistically significant improvement within groups, but not between groups

hard acrylic splint; and UT plus a non-occluding hard acrylic splint. All patients improved over time, and no significant difference between the groups could be found. The authors suggest that clinicians who treat patients with TMD should consider prescribing low-cost nonsplint self-care therapy for most patients.

The methodology of these clinical investigations differed in several important aspects, although all patients had a diagnosis of myofascial TMD pain: in the study by Dao, patients were recruited both by advertisements in the local newspapers and referrals, while in the other three, patients had requested treatment for TMD pain. Pain intensity of the patients at baseline differed considerably in the studies of Dao and Ekberg, being 35 mm in the study by Dao, and 73 mm in the study by Ekberg, assessed on a visual analogue scale. The study by Raphael and Marbach also included patients suffering from widespread pain. In addition, in the studies by Ekberg and co-workers and Truelove and co-workers, patients were instructed to wear their appliances every night, while in the others, patients were instructed to wear the appliance day and night. Thus, comparing the results of these studies seems fairly difficult.

Despite these differences, it seems that most patients suffering from myogenous TMD pain are helped by the incorporation of a stabilization appliance (Türp et al. 2004), and that the stabilization appliance seems to be appropriate and highly recommendable (Schindler and Svensson 2007) in the treatment of TMD patients with myofascial pain.

2.6.2. Other appliances

The resilient appliance, made in a soft plastic material, is a variation of the complete-covering appliances. Clinicians often favour this appliance, because it can be produced quickly and at a low cost. Only a few studies have evaluated the efficacy of these appliances (Wright et al. 1995, Truelove et al. 2006, Nilsson 2010). In two recent studies (Nilsson et al. 2009, Nilsson 2010), a resilient appliance was compared to a hard, palatal, non-occluding appliance in the treatment of 80 recruited TMD pain patients. At the 10-week follow-up, a 30% reduction in TMD pain at its worst was reported on a visual analogue scale (VAS), reported by 61% in the treatment group, and by 46% in the control group. At the 12-month follow-up, 50% in the treatment group and 42% in the control group reported a statistically significant decrease of 30% in characteristic pain intensity (CPI). The conclusion of these RCTs was that there was no difference between the appliances in reducing TMD pain, neither in a short- nor a long-term perspective, and that the resilient appliance seems to be "a treatment modality with poor long-term efficacy in adult patients with TMD".

The relaxation splint is a maxillary splint with contacts only between lower incisors and the splint. It has been claimed that the relaxation appliance is clinically efficient for relieving muscular tension and clinicians often favour the relaxation appliance, especially in the beginning of therapy. There are only few clinical trials on the effect of the relaxation appliance. Clinical signs of TMD patients improved significantly in a stabilization appliance group compared with a relaxation splint group after six weeks

(Dahlström and Haraldson 1985, 1989). In another study, the stabilization appliance gave better relief of both signs and symptoms of TMD compared with a relaxation splint (Siegert and Gundlach 1989). However, the stabilization appliance was fabricated for the mandible and patients were advised to use their appliances as much as possible, except when eating, while Dahlström and Haraldson advised their patients to wear the appliances only at night.

The Nociceptive Trigeminal Inhibition Tension Suppression System (NTI) was introduced in 2001 (Shankland 2001, 2002), aiming mainly at reduction of TTH and migraine. Its specific design, with a single, pinpoint contact on the discluding element, aimed at suppressing the intensity of parafunctional pericranial muscular activity by taking advantage of the jaw-opening reflex. Evidence from RCTs suggest that the NTI device may be successfully used for the management of bruxism and TMDs (Stapelman and Türp 2008, Jokstad 2009). However, to avoid potential undesired effects, this appliance should be chosen only if it is certain the patient will be compliant with follow-up appointments (Stapelman and Türp 2008).

General practitioners often claim that adjustment of a stabilization appliance is a difficult and time-consuming procedure (Lindfors et al. 2006). Due to the prevalence of TMD pain of 6–12% (Von Korff et al. 1988, Dworkin and LeResche 1992, Lipton et al. 1993), there is a need for the general dental practitioner to treat patients with TMD. The design of a stabilization appliance has also sometimes been considered extensive, affecting the comfort and thereby the compliance of the patient (Ekberg and Nilner 2002, 2004).

On the basis of these facts, a new prefabricated appliance was developed (Study I). This appliance includes a front plateau that covers the edges of the incisors and canines with a palatal extension of about 1 cm. The frontal plateau allows both occlusal and articulation contacts. This new appliance should be compared with a well-accepted occlusal appliance. According to the above-mentioned reviews, the most extensively tested appliance is the stabilization appliance.

2.7. Evaluation of treatment outcome

When evaluating treatment outcome, a structured and well-designed evaluation process is essential. A standard set of outcome measures is important to be able to compare studies of different treatment modalities. According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, IMMPACT (Turk et al. 2003), clinical trials and studies on efficacy and effectiveness in different chronic pain conditions should consider six core domains: 1) pain, 2) physical functioning, 3) emotional functioning, 4) participant ratings of improvement and satisfaction with treatment, 5) symptoms and adverse events, and 6) participant disposition. There may be exceptions to the inclusion of all these domains. When this occurs, the rationale for not including domains should be provided. However, these recommendations should not be considered a requirement for approval of product applications, nor must a treatment demonstrate statistically significant effects

in all the relevant core domains to establish evidence of its efficacy. In a later consensus statement (Dworkin et al. 2008), as a result of considering methodological issues and research results relevant to determining the clinical importance of changes in the specific outcome measures previously recommended, four core chronic pain outcome domains were recommended for use in performing clinical trials on chronic pain conditions: 1) pain intensity, 2) physical functioning, 3) emotional functioning, and 4) participant ratings on overall, global improvement.

In order to be transparent for critical evaluation of clinical trials, adverse events or effects of treatment and participant disposition should be measured. The guidelines of the Consolidated Standards of Reporting Trials, CONSORT (Moher et al. 2005), were developed to serve as a guide to improve reporting results of RCTs. Information about the 1) recruitment process, 2) excluded participants and reasons for exclusion, 3) subjects who refused participation and why, 4) other deviations such as concomitant treatment, and 5) withdrawal of patients at follow-ups and reasons for this, should be described when reporting RCTs.

Regarding long-term follow-up studies of TMD pain, attention must be paid to the natural time flow influencing the TMD conditions. Further, the placebo response to different treatment modalities of TMD is also well known. Every treatment for pain contains a placebo component, which may sometimes be powerful.

2.8. Efficacy versus effectiveness in the design of clinical trials

Randomized Clinical Trials are the golden standard in evaluating the effects of treatment. Clinicians often distinguish between the efficacy and the effectiveness of an intervention. Efficacy trials (explanatory trials) determine whether an intervention produces the expected result under ideal conditions. Effectiveness trials (pragmatic trials) measure the degree of beneficial effect under “real world” clinical settings (Godwin et al.2003). Gartlehner and co-workers (2006) proposed and tested seven hallmarks of study design to create a tool that can help researchers to distinguish more readily and more consistently between efficacy and effectiveness studies. Based on this tool, criteria for designing effectiveness studies have been prepared by the RTI-International (Research Triangle Institute, University of North Carolina Evidence-based Practice Center, Triangle Park, NC, USA). These criteria are: 1) populations in primary care, 2) less stringent inclusion criteria, 3) health outcomes, 4) long study duration; clinically relevant treatment modalities, 5) assessment of adverse effects, 6) adequate sample size to assess a minimally important difference from a patient perspective, and 7) intention-to-treat analysis. On the basis of the rationale that the authors want to identify effectiveness studies reliably with minimal false positives (i.e. high sensitivity), a cut-off of six criteria produced the most desirable balance between sensitivity and specificity.

Effectiveness studies are of great value because of their clinical relevance for general practitioners. Previous studies on occlusal appliances are mainly efficacy trials set up under ideal conditions, while effectiveness studies are few.

3. AIMS

A commonly used treatment modality within dentistry for treating TMD patients consists of the occlusal appliances, and of these the stabilization appliance is the most extensively studied one. As general practitioners often claim that adjustment of a stabilization appliance is difficult and time-consuming, there seems to be a need for an easy and less time-consuming treatment modality, parallel to the stabilization appliance. Thus, the aims of the present study were:

- To compare the short- and long-term effectiveness of a prefabricated appliance with that of a stabilization appliance in the treatment of patients with myofascial TMD pain.
- To compare the short- and long-term effectiveness of a prefabricated appliance with that of a stabilization appliance regarding frequency and intensity of headache in patients with myofascial TMD pain.
- To evaluate the effect of treatment with occlusal appliances on salivary parameters in patients with myofascial TMD pain.

4. HYPOTHESES

- The effectiveness of a prefabricated appliance is similar to that obtained with a stabilization appliance in the treatment of patients with myofascial TMD pain in both a short- and long-term perspective
- The effectiveness of decreasing the intensity and frequency of headache in patients with myofascial TMD pain in a short- and long-term perspective is similar in patients treated with a stabilization appliance and with a prefabricated appliance.
- Treatment of myogenous TMD-related pain and pain associated with stress would lead to a decrease in saliva cortisol and IgA levels, with no difference in outcome between the two occlusal appliances.

5. SUBJECTS AND METHODS

5.1. Patients

The study was performed during the period of February 2005 to August 2007 as a multicentre study in Malmö, Sweden, and Turku, Finland. Sixty-six patients were selected from 1149 patients referred for treatment of TMD to the Department of Stomatognathic Physiology, Faculty of Odontology, Malmö University, Sweden, and the Department of Stomatognathic Physiology, Faculty of Medicine, Turku University, Finland. On the basis of the information in the referrals, 203 patients were clinically screened according to the inclusion and exclusion criteria. The procedure is presented in Figure 1. Of the nine patients declining to participate, eight reported inability to follow the schedule of appointments, and one ongoing dental treatment. Of the 66 patients initially meeting the inclusion and exclusion criteria, Figure 2, one patient was rediagnosed with arthrogenous pain and thereby excluded from the study.

According to a power calculation, made before the beginning of the study, the inclusion of at least 22 patients in each group would provide a statistical power slightly above 90% for obtaining statistical equivalence. Equivalence means within 15 units in a two-tailed test at the 5% level if the true success probability in the group treated with a prefabricated appliance is the same or differs from that of the group treated with a stabilization appliance.

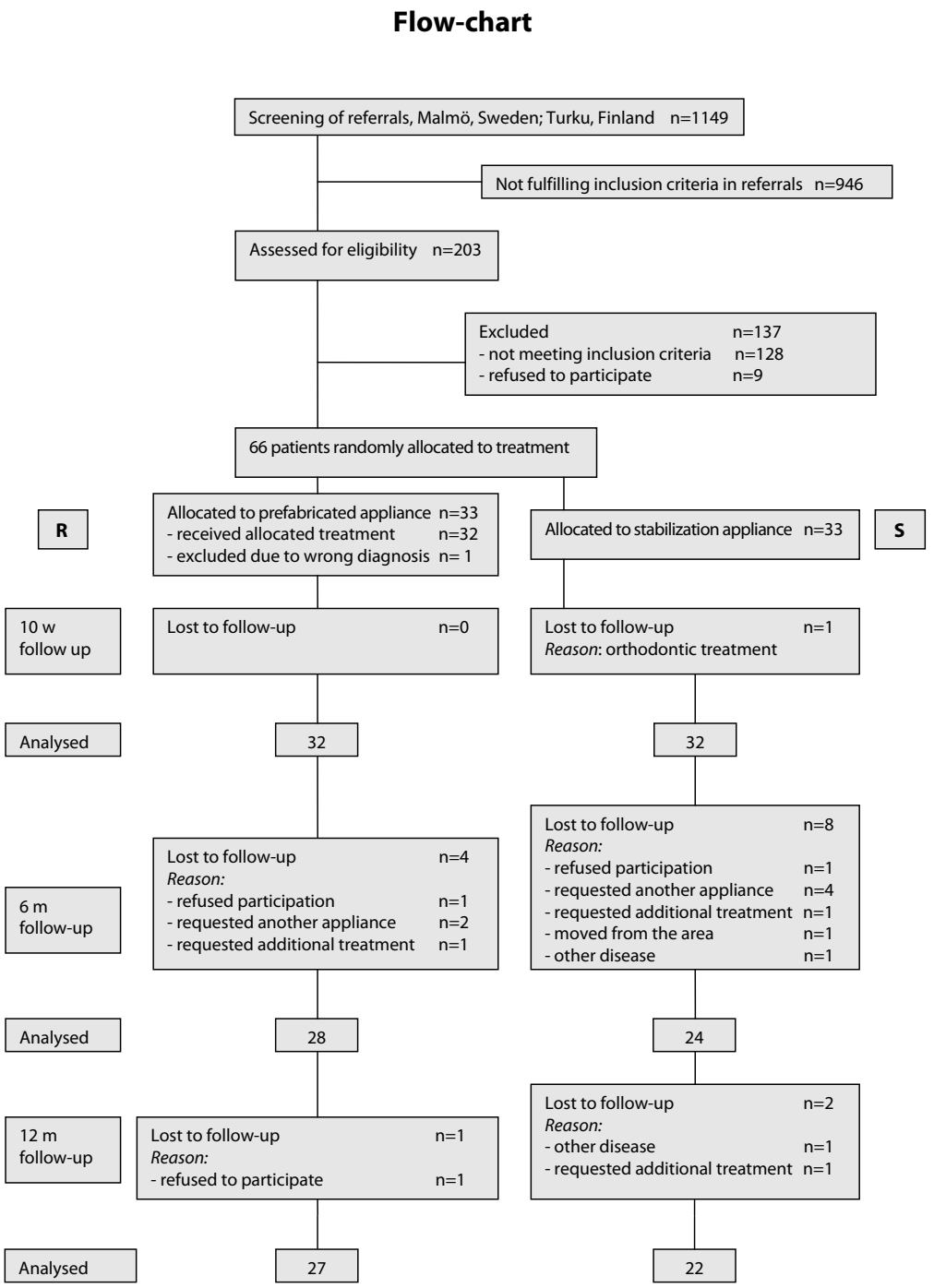


Figure 1. Flow-chart
R = prefabricated appliance; S = stabilization appliance

Inclusion criteria

- age ≥ 18 years
- pain of muscular origin with or without limited opening according to the Research Diagnostic Criteria for TMD of Dworkin and LeResche
- self-assessed worst myofascial pain of at least 4 on a 0-10 graded numeric rating scale, NRS
- duration of pain at least 3 months
- ability to make appointments for saliva collection at the same time of the day ±1 h (Study II)

Exclusion criteria

- TMJ pain verified by interview or clinical examination
- presence of complete dentures
- symptoms related to disease in other components of the stomatognathis system (e.g. toothache, neuralgia)
- diagnosis of whip-lash
- diagnosed systemic muscular or joint disease (e.g. fibromyalgia, rheumatoid arthritis)
- history of psychiatric disorders
- periodontal problems
- previous treatment with an occlusal appliance
- presence of idiopathic orofacial pain

Figure 2. Inclusion and exclusion criteria of the study

5.2. Randomization

The study was performed as an RCT. Patients were randomly allocated to one of two groups: one group was treated with a prefabricated partial-covering appliance (R), and the other was treated with a complete-covering stabilization appliance (S). One independent person, D2 (Fig.3), at each clinic carried out the randomization using 10 series of consecutively numbered, sealed, opaque envelopes. Each envelope contained a treatment specification, five with the symbol R for prefabricated appliance, and five with the symbol S for stabilization appliance. The last series included six envelopes, three for each treatment modality. This randomization procedure was repeated until 66 patients were included in the study. One patient was excluded due to an incorrect diagnosis. The number of patients recruited was higher than the sample size originally planned to compensate for eventual drop-outs.

Visits (V) before treatment and at 6- and 10-week, and 6- and 12-month follow-ups, performed by dentists A and B and a dental assistant, D1. Randomization was carried out by an independent person, D2.

		Examiners
V0	History questionnaire	A
	Saliva sampling	D1
V1	Clinical examination, information and reassurance, impressions	A
	Clinical examination, saliva sampling	D1
	Randomization	D2
V2	Appliance therapy starts	B
V3	Appliance check-up and adjustment	B
V4	Follow-up, 6 weeks:	
	History questionnaire	A
	Clinical examination, saliva sampling	D1
	Appliance check-up and adjustment	B
V5	Follow-up, 10 weeks:	
	- as 6-week follow-up	
V6	Follow-up, 6 month:	
	History questionnaire	A
	Clinical examination	D1
	Appliance check-up and adjustment	B
V7	Follow-up, 12 month	
	- as 6-month follow-up	

Figure 3. Flow-chart of the study set-up.

5.3. History taking and clinical examination

5.3.1. Study set-up

The history taking and the clinical examination according to RDC/TMD were performed at baseline and at all follow-ups. A single examiner at each university, dentist A, blinded to the treatment groups, performed the clinical investigations and a trained dental assistant, D1, performed a clinical examination, including a registration of opening capacity and recording of PPT, before treatment and at all follow-ups. Examiner A informed the patients about the lack of a clear-cut cause of their myofascial pain and about contributing factors. They were reassured and informed about the nature of TMD and the relationship between muscle fatigue, muscle pain and the psychophysiologic aspects of stress, and how to self-monitor TMD symptoms. Examiners A were calibrated to the recommended pretraining study site protocol for the set-up of the use of RDC/TMD (www.rdc-tmdinternational.org). To exclude odontogenic reasons for the orofacial pain a Panoramic Radiography examination was performed. The treatment with an occlusal appliance was performed by dentist B. Dentist B, a general practitioner at both clinics, not involved in the examination at baseline or at follow-ups, delivered, adjusted and evaluated the use and wear of appliances. The general practitioners were instructed and trained together in the individual fitting of the prefabricated appliance in an identical way before the start of the study. All participants gave their written consent.

5.3.2. History taking

A history questionnaire according to RDC/TMD (Dworkin and LeResche, 1992) including a one-week pain diary was filled in by the patients at baseline and at all follow-ups.

Patient characteristics such as age, gender, ethnicity, marital status, level of education, occupation, place of residence, and duration of TMD were registered and studied.

Frequency of myofascial TMD pain was recorded as 1) occasionally, 2) recurrent, or 3) persistent. The intensity of myofascial TMD pain during the preceding six months was assessed on a numeric rating scale, NRS (Farrar et al. 2001), with the end-points 0 - no pain, and 10 - pain as bad as could be.

The pre-treatment questionnaire included four questions about both occurrence and frequency of headache during the preceding six months on a verbal scale as follows: 1=continuous; 2=recurrent; 3=rarely. Patients reporting recurrent headache specified it as follows: 1=once a month; 2=once a week; 3=at least 15 times a month. The intensity of headache during the preceding six months was assessed on NRS (Farrar et al. 2001), with the end-points 0 - no pain, and 10 - unbearable pain, while intensity of headache during the month prior to the follow-ups was registered on VAS (Seymor et al. 1985) with the end-points 0 - no pain, and 100 mm - unbearable pain. For statistical analysis

and comparison with NRS baseline data, VAS was transformed to a scale of 0-10 using the following conversion rules: 0-4 mm=0; 5-14 mm=1; 15-24 mm=2.....95-100 mm=10.

Daily pain intensity during one week at rest, on mouth opening and on chewing was recorded on VAS, with the endpoints “no pain” and “very severe pain” (Seymor et al. 1985), in addition to the history questionnaire used before treatment and at all follow-ups.

At the follow-ups, improvement in overall subjective symptoms was measured according to a 6-point verbal rating scale: 0 = symptom-free, 1 = much better, 2 = better, 3 = unchanged, 4 = worse, 5 = much worse. Patients also determined the subjective reduction of myofascial pain on a VAS scale with the endpoints “no reduction” and “complete reduction”, compared to before onset of treatment. The patients were asked to report any kind of discomfort associated with the appliance therapy and how often they used the appliance (0 = every night, 1 = several nights a week, 2 = when necessary, 3 = not at all).

On the basis of the history questionnaire of RDC/TMD, the patients were classified for Graded Chronic Pain, GCP, severity (Von Korff et al. 1992) as follows: Grade 0 = no TMD pain in the previous six months; Grade I = low disability – low intensity pain; Grade II = low disability – high intensity pain; Grade III = high disability – moderately limiting; Grade IV = high disability – severely limiting.

Functional limitation of the jaw was assessed over time with the Jaw Function Limitation Scale (JFLS-20) (Ohrbach et al. 2008). JFLS-20, consisting of three constructs, mastication, vertical jaw mobility, and verbal and emotional expression, is determined by twenty questions recorded on a numeric rating scale from 0-10 (0 = no limitation and 10 = maximal limitation), and reported as summary scale scores.

The changes in psychological status, depression and nonspecific physical symptoms (NSPhS), were assessed using the modified SCL-90-R instrument in Axis II (Dworkin and LeResche 1992), consisting of 20 questions indicating depression and 12 indicating non-specific physical symptoms with the classifications normal, moderate and severe.

Awareness of grinding or clenching during the day and at night, and pain from neck and shoulders were registered. The patients also answered questions at baseline about self-assessed stress regarding family, home, work, economy, relationships, general health, and stress in general, according to a verbal scale (0-3; 0 = not at all, 1 = very little, 2 = to some extent, 3 = very much). At the various follow-ups the patients were asked about the frequency of their use of the appliance by means of a verbal scale: every night, several nights a week, or when necessary. The patients reported at baseline the type of regular medication intake.

5.3.3. Clinical examinations

Clinical examinations according to RDC/TMD (Dworkin and LeResche, 1992) were completed at baseline and at all follow-ups.

Before treatment and at all follow-ups a trained dental assistant, D1, performed a clinical examination, including registration of unassisted mouth opening capacity without pain and maximal assisted opening, and recording of PPT using an electronic algometer (Somedic AB, Farsta, Sweden). The tip of the algometer had a surface of 1 cm² and a rate of pressure increase of approximately 30 kPa/sec. The PPT was determined as the point at which stimulus applied to the skin changed from a pressure sensation into a sensation of pain. PPTs were assessed bilaterally at the masseter muscle and the anterior temporal muscle (Svensson et al. 1995) and on the right hand. The PPT was recorded twice on each side with an interval of two minutes between, and the mean value of two recordings was used as the baseline value. The order of assessments was the same for all recordings, starting with the muscles on the right, then the left side, and ending with the reference point.

5.4. Occlusal appliances

The prefabricated appliance, made of polymethylmethacrylate, included a front plateau covering the edges of the incisors and canines with a palatal extension of about 1 cm (Fig.4). The frontal plateau allows both occlusal and articulation contacts. The buccal side of the appliance has two extensions widening the dimension of the appliance and facilitating removal. The appliance is individually fitted with a self-curing silicon material, polyvinylsiloxane, placed inside the appliance and attached with an adhesive. The adjustment of the appliance aims at achieving contacts in the centric relation. In lateral excursions, contacts on the canines or frontal group contacts, as well as symmetrical contacts at protrusion, were achieved.

The stabilization appliance (Fig.5) had a smooth, flat surface with supporting teeth in contact and was adjusted in the centric relation. The appliance also had a canine-protected articulation or group contacts of frontal teeth. At protrusion, the appliance had bilateral, symmetrical contacts between canines. Both appliances were recommended to be used every at night for 10 weeks, and after that, when needed. The occlusal appliances were made, adjusted and delivered by the general practitioner, B. The comfort, patients´ acceptance and the function of the appliance were checked within two weeks, and the same procedure was repeated at all follow-ups by the general practitioner. At follow-ups, need for additional adjustment was registered. When the participants were evaluated, a dental nurse instructed the patients to neither discuss the treatment with examiner A, nor show their appliances as long as the examiner was present.

Patients not satisfied with the treatment outcome and demanding other treatments were offered the other appliance therapy. All patients had the same number of visits.

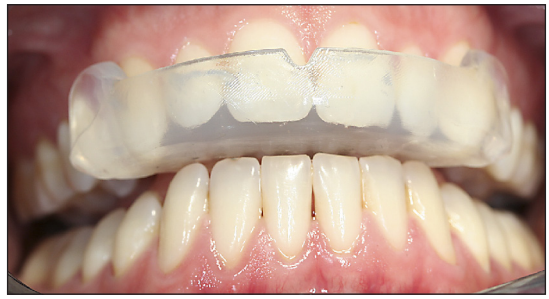


Figure 4. Prefabricated appliance (R), frontal view

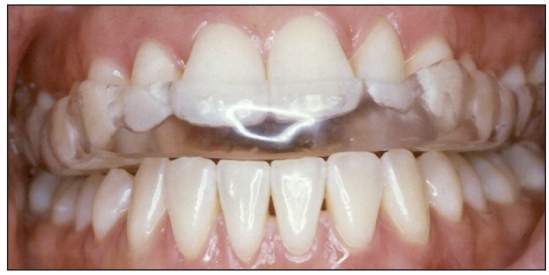


Figure 5. Stabilization appliance (S), frontal view

5.5. Adverse effects/Testing intra- and inter-examiner variation of measurement of over-bite

For assessment of adverse events, vertical over-bite was measured to the nearest 0.5 mm. To estimate the precision of the measurements, 22 patients were examined by two independent clinical examiners. The reliability of measurement was tested both intra- and inter-individually in two different ways.

The Dahlberg formula (Dahlberg 1948) and the intraclass correlation coefficient (Shrout and Fleiss 1979) were used to measure the error of overbite measurements. The intraclass correlation coefficient was 0.99 for both examiners. Interindividually, the coefficient was 0.98. Method errors according to the Dahlberg formula ranged from 0.3-0.5mm interindividually, and were 0.2 mm for both examiners.

5.6. Study II – saliva sampling and analyses

The inclusion criterion for participation in Study II was the ability to make appointments for saliva collection at the same time of the day +/- one hour because of the diurnal rhythm of salivary cortisol (Saliva Diagnostics 2006). Thirty-nine patients fulfilled the inclusion criterion and all of them completed the study. Due to the time of the patient`s visit, 20 of these 39 patients had their samples collected in the morning before 10 am., and 19 after 10 am.

Paraffin- stimulated saliva samples were collected from the patients before and after treatment with the two different occlusal appliances. Paraffin-stimulated saliva was chosen to obtain reproducible samples for determination of three salivary variables. This has also been approved in the manual of Saliva diagnostics (Saliva Diagnostics 2006). Samples were collected at visits 0 and 1 with a one-week interval preceding appliance treatment, and during follow-ups at 6 and 10 weeks. Patients were asked not to consume any food or drink one hour before the saliva collection; only water was allowed. To stabilize the flow rate, saliva was first collected for half a minute with the patient in an upright position and the amount obtained was discarded. Saliva was collected into a graduated tube for 3 minutes while the patient was in a normal sitting position. The saliva volume was measured without delay.

Of the saliva collected, three ml was transferred with a pipette into a disposable test tube and deep frozen to -70 °C. Before analyses the saliva samples were thawed and centrifuged (10 000 x *g*, 10 min, +4 °C). Cortisol was assessed from the samples using the Cortisol Spectria RIA Kit (Orion Diagnostica, Espoo, Finland) according to the instructions of the manufacturer. Salivary total IgA was assayed using a 'trapping-antibody'-type enzyme immunoassay, described earlier (Lehtonen et al. 1984). In this method, immobilised isotype-specific antihuman immunoglobulins catch sample antibodies, which are then detected by enzyme-conjugated antibodies. Rabbit heavy chain specific anti-IgA, -IgG and -IgM and the corresponding reagents conjugated with horseradish peroxidase came from Dako A/S (Glostrup, Denmark). The immunoglobulin standards were purified from human serum (Dako). The substrate for the enzyme immunoassay, 1,2-phenylene-diamine, was purchased from Sigma Chemical Co., St. Louis, MO, USA.

5.7. Outcome measures

5.7.1. Studies I, III and IV

In determining outcome measures, the four domains according to IMMPACT recommendations, i.e. overall, global improvement, pain intensity, physical functioning, and emotional functioning were considered. Thus, primary outcome measures were: (1) improvement in overall symptoms, assessed on a verbal scale as follows: "no change" to "worse", "better" to "symptom-free", and "much better" to "symptom-free" (Studies I & III), (2) 50% and 30% reduction in pain according to the VAS scale (Studies I & III), (3) physical functioning according to GCP, and functional limitation of jaw (Study III), and (4) emotional functioning (Study III).

Other outcome measures were: (a) reported frequency, according to a verbal scale "no/rarely" or "continuous/recurrent", and intensity, assessed on the NRS, of headache (Study IV), (b) association between emotional functioning and headache (Study IV), (c) pain on rest and movement of jaw assessed on VAS (Study I & thesis), (d) PPT of the anterior temporalis muscle and masseter muscle (Studies I & III), and (e) opening capacity of mouth (Study III).

Additional outcome measures included changes in vertical overbite after using the appliance. Wear and use of the appliances were registered, as well as need for adjustment of the appliances at follow-ups.

5.7.2. Study II

The outcome measures were influence of outcome of appliance therapy on stress-related saliva parameters, cortisol and IgA, and flowrate.

5.8. Statistical methods

The chi-square test was used for comparison of the distribution of variables in different groups of patients on a nominal scale, and the Mann-Whitney U test for the variables measured on an ordinal and continuous scale. These tests were used to determine the significance of differences between groups (Studies I, III and IV).

For comparison within groups, the McNemar test was used for dichotomic variables and Wilcoxon´s signed rank test for analysing changes between baseline data and follow-up measurements, and for the variables measured on an ordinal and continuous scale (Studies I, III and IV).

The Mann-Whitney U test was used of variables measured on a nominal and a continuous scale for analysing the difference in change between groups (Studies I, III and IV).

The variables (Study II) were compared at each examination point between the groups using independent samples t-test. For longitudinal comparisons (before and after treatment) the analysis of variance for repeated measures was used. The level of statistical significance was set at $p < 0.05$. Cortisol and IgA values were calculated according to reported stress levels (RDC/TMD) using the chi-square test.

Differences at the 5% level of probability were considered statistically significant. Statistical analyses were done using SPSS 16.0 and 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Approval of the study design

The study design was approved by the Ethic Committees of Lund and Turku Universities (permission H4 846/2004 [Lund] and 19.10.2004 §305 [Turku]).

6. RESULTS

6.1. Baseline data of the study

The demographic data of the patients are shown in Table 3. No differences were found in age, gender, ethnicity or other demographic data between the two groups at baseline.

Table 3. Demographic data of the 65 myofascial TMD pain patients before treatment (Study I, Table 1) R=prefabricated appliance; S=stabilization appliance.

	R (n=32)	S (n=33)
Gender		
Female	27	31
Male	5	2
Age (y)		
Mean	37	36
Median	38	36
Min-max	20-63	18-71
<20	0	4
20-40	19	17
>40	13	12
Ethnic origin		
Scandinavia	28	24
Other European countries	3	6
Asia	1	3
Marital status		
Married	20	20
Divorced	4	4
Never married	8	9
Highest level of education		
Elementary school	4	4
High school	18	18
College	10	11

Figures depict number of subjects

Symptoms and signs are presented in Table 4. Myofascial TMD pain with a duration of 6 months or more was reported by 98% (64/65) of all patients, while the rest of the patients, 2%, had pain for 3 to 6 months. Of all patients, 95%, reported their myofascial TMD pain to be "recurrent-persistent", and of these, 44% (27/62) reported "persistent" pain. The mean NRS value for the worst myofascial TMD pain was 7.6 for all patients. Ninety-four percent (61/65) of all patients reported suffering from headache at baseline. The mean NRS value for the intensity of headache was 5.7 for all patients. The majority, 71% (46/65) of all patients, reported their headache to be "recurrent-continuous". In both groups, altogether 72% of the 40 patients reporting recurrent headache, had a headache frequency of less than 15 times a month. There were no differences between the groups regarding either myofascial TMD pain or headache. Clenching and/or grinding during daytime was reported by 68% (44/65) of all patients, while the figure for night-time was

75% (49/65). All patients reported tenderness to palpation of masticatory muscles, with 94% (60/65) reporting this tenderness as mild to moderate, and 65% (42/65) reporting it as severe. Pain in neck and shoulders was reported by 92% of all patients. There were no differences between the groups regarding muscle tenderness and pain in neck and shoulders. At baseline, 68% of all patients reported overall stress to some or a great extent.

Table 4. Distribution of reported myofascial TMD pain and headache, awareness of parafunctions, registered palpatory tenderness of the masticatory muscles, pain from neck and shoulders before treatment and self-reported stress.
NRS = numeric rating scale; R = prefabricated appliance; S = stabilization appliance

	R (n=32)	S (n=33)
Duration of myofascial pain (mo)		
Mean	80	50
SEM (+/-)	20	9
Min-max	3-480	6-240
3 to 6 mo	1	0
≥ 6 mo	31	33
NRS at the examination		
Mean	4.0	5.2
SEM (+/-)	0.43	0.46
NRS worst		
Mean	7.9	7.4
SEM (+/-)	0.27	0.35
NRS on average		
Mean	5.6	5.8
SEM (+/-)	0.30	0.35
Frequency of myofascial pain (n)		
One time	2	1
Recurrent	16	19
Persistent	14	13
Intensity of headache NRS		
Mean	5.3	6.1
SEM (+/-)	0.54	0.47
Frequency of headache (n)		
No headache	3	1
Rarely	6	9
Recurrent		
- once a month	2	7
- once a week	11	8
≥ 15 times a month	7	4
Continuous	3	4
Awareness of grinding and clenching (n)		
- night-time	27	22
- day-time	22	22
Palpatory tenderness in masticatory muscles (n)		
Mild to moderate	30	30
Moderate to severe	18	25
Severe	18	24
Pain from neck and shoulders (n)	29	31
Stress in general (n)		
to some extent/very much	17	27

There were no significant differences between the groups for any variable
n = number of subjects

The diagnoses of the patients are presented in Table 5. Out of all myofascial TMD pain patients, 25% (16/65) also had a disc displacement, and 6% (4/65) had a diagnosis of osteoarthrosis. No differences were found in the subdiagnosis of TMD between the groups.

Table 5. Diagnoses according to RDC/TMD in 2 patient groups at baseline (Study I, Table 3). R = prefabricated appliance; S = stabilization appliance

Diagnosis	R (n=32)	S (n=33)	Total (n=65)
Myofascial pain			
Without limited opening	21	22	43
With limited opening	11	11	22
Disc displacement			
With reduction	6	10	16
Without reduction	0	0	0
With limited opening	0	0	0
Without limited opening	0	0	0
Arthralgia/osteoarthritis	0	0	0
Osteoarthrosis	3	1	4

Figures depict number of subjects

6.2. Short- and long-term treatment results concerning myofascial TMD pain (Studies I and III)

Up to 10 weeks of appliance therapy none of the patients expressed a need for or demanded additional treatment or another occlusal appliance. Sixty-four patients attended the 10-week follow-up, 52 patients the 6-month follow-up, and 49 the 12-month follow-up (Fig. 1). The number of drop-outs was five in the prefabricated appliance (R) group, and 11 in the stabilization appliance (S) group at the 12 months follow-up. Altogether, the share of drop-outs was 23%. When comparing the drop-outs with those completing the study, no differences could be found at baseline regarding either myofascial pain and headache, or demographic data.

Overall improvement in pain

According to the 6-point rating scale, a positive improvement in overall subjective symptoms was registered in both groups, with no differences between groups, at the follow-ups (Table 6). Overall improvement “better”, “much better”, or “symptom-free” was observed in 84% in the R group and in 79% in the S group at the 10-week follow-up, and remained similar during the follow-up period, with 81% improvement in the R and 64% in the S group at the 12-month follow-up.

Pain intensity

A comparable pain reduction in both groups, without differences between the groups, was observed at the follow-ups, compared to baseline. At 10 weeks, 70% of all patients reported a 30% reduction in worst pain, and 55% reported a 50% reduction. The reported pain level did not show further improvement during the follow-up, the 12-month results showing percentages of 72% and 63%, respectively (Table 6).

Table 6. Number of patients reporting reduction of pain and overall changes in symptoms at 10 weeks, and at 6 and 12 months.
a) Reduction of worst reported myofascial TMD pain.
b) Overall changes in subjective symptoms, according to a 6-point rating scale: compared to baseline values.
VAS=visual analogue scale; R=prefabricated appliance; S=stabilization appliance

TMD pain	10 weeks		6 months		12 months		Significance level
	R	S	R	S	R	S	
a) Reduction of worst reported pain (VAS)	(n=32)	(n=33)	(n=32)	(n=33)	(n=32)	(n=33)	
30% pain reduction	23	22	23	22	26	21	NS
50% pain reduction	21	18	22	21	24	17	NS
b) Overall changes in subjective symptoms:	(n=32)	(n=32)	(n=28)	(n=24)	(n=27)	(n=22)	
"no change" to "much worse"	4	6	2	1	1	1	NS
"better"	14	14	11	11	10	9	NS
"much better" to "symptom-free"	13	12	15	12	16	12	NS

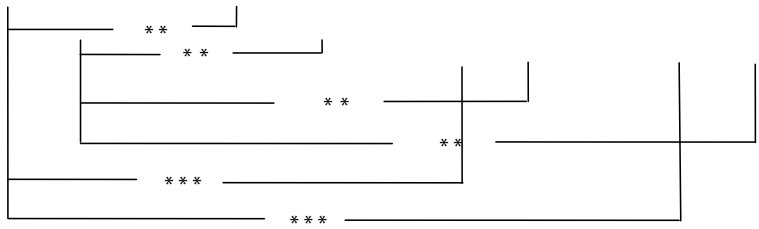
Chi-square test
There was no statistically significant (NS) difference between groups R and S ($p \geq .05$)
Figures depict number of subjects

Physical functioning

The distribution of Graded Chronic Pain in the R and S groups at baseline and at follow-ups is presented in Table 7. Significant changes to a lower grade, when compared to baseline, were observed in both R and S groups ($p \leq .01$ for R group at 10-week follow-up and $p \leq .001$ at 6- and 12-month follow-up; $p \leq .01$ for S group at all follow-ups), without any difference between the groups. In the R group a significant decrease ($p \leq .01$) was noted at the 12-month follow-up, compared to the10-week follow-up.

Table 7. Distribution of Graded Chronic Pain at baseline, at 10 weeks and at 6- and 12- month follow-ups.
Grade 0 = no TMD pain in the previous 6 months; Grade I = low disability - low intensity pain;
Grade II = low disability - high intensity pain; Grade III = high disability - moderately limiting;
Grade IV = high disability - severely limiting.
R= prefabricated appliance; S = stabilization appliance

	Baseline		**10 weeks**		**6 months**		**12 months**	
	R n=32	S n=33	R n=32	S n=32	R n=28	S n=24	R n=27	S n=22
Grade 0	-	-	-	-	1	-	3	-
Grade I	10	11	21	17	19	19	20	16
Grade II	18	15	11	12	6	3	4	4
Grade III	4	6	0	3	2	1	-	2
Grade IV	-	1	-	-	-	1	-	-



Wilcoxon signed ranks test .*p ≤.05; **p ≤ .01; ***p≤.001
Figures depict number of subjects

There were no statistically significant differences at baseline between the groups concerning limitation scores in jaw function. A statistically significant reduction in mastication and vertical jaw mobility, compared to baseline, was observed within but not between groups at all follow-ups (Fig.6). Regarding verbal and emotional expression, no statistically significant decrease, compared to baseline, was detected until the 6- and 12-month follow-ups.

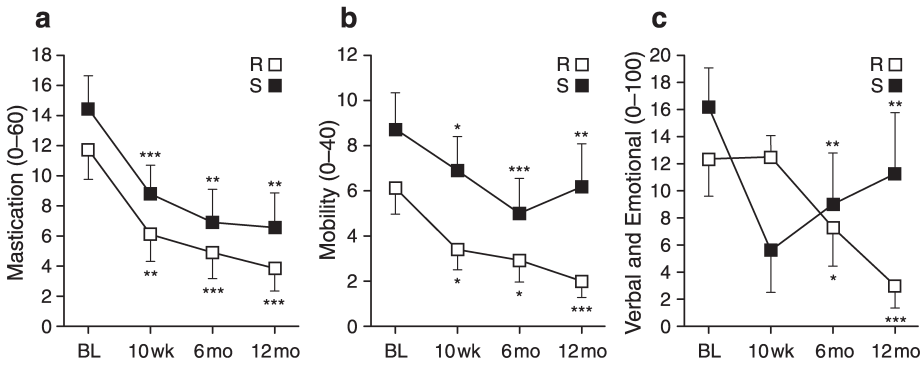


Figure 6. Differences between summary scale scores (mean and SEM) for each construct in the Jaw Functional Limitation Scale-20-Item Version assessed at the 10-week, at the 6- and 12-month follow-ups, and compared to baseline.
a) mastication (Mastication)
b) vertical jaw mobility (Mobility)
c) verbal and emotional expression (Verbal and Emotional)
R= prefabricated appliance; S= stabilization appliance
Wilcoxon signed ranks test: *P≤ .05; **P≤ .01; ***P .001

Emotional functioning

The scores for NSPhS and depression at baseline and at follow-ups in the R and S groups are presented in Figure 7. At the 10-week follow-up, depression showed a statistically significant decrease in the R group compared to baseline. During the 6- and 12-month follow-ups, both NSPhS and depression decreased significantly within the groups compared to baseline, but there were no differences between the groups.

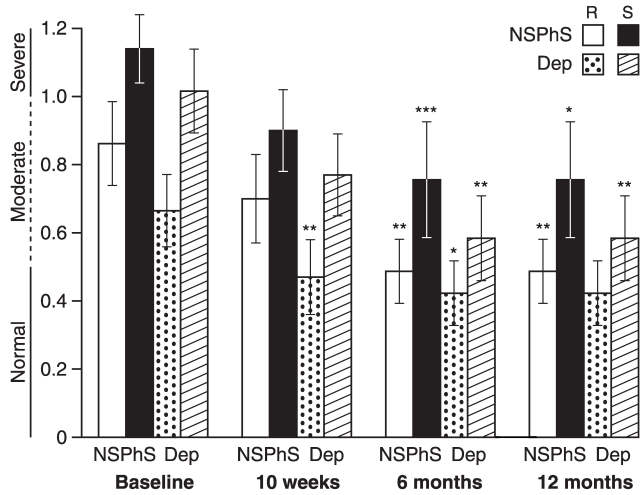


Figure 7. Nonspecific physical symptoms (NSPhS) and depression (Dep) (SCL-90-R) scores (mean and SEM) assessed at baseline and compared with 10-week, and 6- and 12-month follow-ups.
R= prefabricated appliance; S= stabilization appliance
Wilcoxon signed ranks test: *P≤ .05; **P≤ .01; ***P≤ .001

Additional outcomes

The registered pain, VAS, at rest and movement (opening and chewing) had improved statistically significantly (P≤ .05) at all follow-ups (Fig. 8).

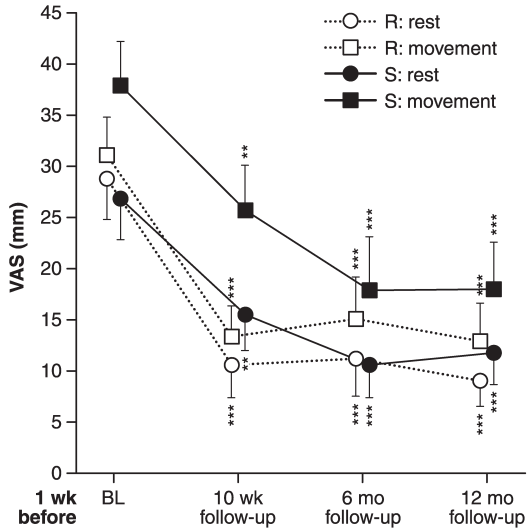


Figure 8. Mean daily pain registration for a 1-week period on VAS at rest and on movement (opening and chewing) in both groups, assessed before the start of the treatment and before the 10-week, and the 6- and 12-month follow-ups.
R= prefabricated appliance; S= stabilization appliance
Wilcoxon signed ranks test: **P≤ .01; ***P≤ .001

A statistically significant increase in PPT was found in both groups on the right side of the anterior temporal muscle at the 10-week follow-up, and on the left side of the anterior temporal muscle at all follow-ups (Fig. 9). Furthermore, there was a significant difference in the S group on the right anterior temporal muscle between baseline and the 6-month follow-up (P≤ .05). No statistically significant changes in PPT of the masseter muscle could be found in either group.

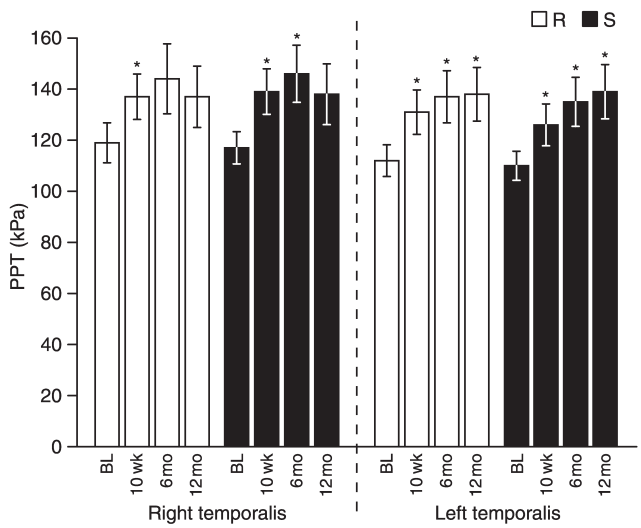


Figure 9. Algometer registration (pressure pain threshold and SEM in kPa) in both groups at baseline and at the 10-week, and 6- and 12- month follow-ups.
R= prefabricated appliance; S= stabilization appliance
Wilcoxon signed ranks test: *P≤ .05; **P≤ .01; ***P≤ .001

Mouth opening showed no statistically significant differences between or within the groups during the follow-up period. The unassisted opening capacity without pain, the mean of both groups, increased from 41.8 mm at baseline to 43.7 mm at 12 months, while the assisted opening capacity remained similar at baseline (53 mm) and at the 12-month follow-up.

Adverse effects

At the 6-month follow-up, one patient in the R group with a vertical overbite of -1 mm at baseline, had an overbite of -3 mm. This patient was given a stabilization appliance, and no further increase in vertical overbite could be registered at the 12-month follow-up.

Use and need of adjustment of occlusal appliances during the study

Up till 10 weeks patients were instructed to use their appliances every night. At the 6-month follow-up, 39% of the patients in the R group reported that they used their appliance every night, compared with 25% in the S group (Table 8). By 12 months, the use had decreased to 33% in the R group and 14 % in the S group. At the 12-month follow-up, 33% in the R group and 50% in the S group used their appliances when necessary. There was no statistical difference between the groups in need of additional adjustment at follow-ups.

Table 8. Frequency of use, additional adjustment and wear of the appliances at 10 weeks and 6 and 12 months in the prefabricated (R) and stabilization (S) appliance group.

	10 weeks		6 months		12 months	
	R (n=32)	S (n=32)	R (n=28)	S (n=24)	R (n=24)	S (n=22)
Frequency of use						
every night	26	21	11	6	8	3
several n/w	1	5	8	7	8	8
when necessary	5	6	7	9	8	11
Additional adjustment of appliances	11	17	15	16	16	14
Wear						
slight	7	7	7	6	8	7
moderate	0	0	0	0	1	1
severe	0	0	0	0	0	0

Figures depict number of subjects

Influencing factors

Use of appliances, overall reported stress, intensity of myofascial pain, and reported pain in neck and shoulders were tested for an eventual association with headache. None of the above-mentioned factors was found to be associated with the outcome decrease in headache in neither group. The same outcome was found regarding social factors, such as sick leaves, general health, social status, and educational level as reported by the patients.

6.3. Short- and long-term treatment results on headache (Study IV)

Frequency of headache

There were no differences at baseline between the groups regarding frequency or intensity of headache. Frequency of headache decreased statistically significantly ($p \leq .01$), with no difference between groups, compared to baseline at all follow-ups in both groups (Table 9). The fluctuation of frequency of headache is illustrated in Figure 10.

Table 9. Reported frequency of headache at baseline, 10 weeks, 6- and 12-month follow-ups (Study IV, Table 1)
R = prefabricated appliance; S = stabilization appliance

	Baseline		10 weeks		6 months		12 months	
	R (n=32)	S (n=33)	R (n=32)	S (n=32)	R (n=28)	S (n=24)	R (n=27)	S (n=22)
No headache	3	1	6	4	5	2	4	1
Rarely	6	9	12	18	14	17	16	17
Recurrent								
- once a month	2	7	2	3	2	2	0	2
- once a week	11	8	5	5	2	2	4	1
- ≥15 times a month	7	4	4	2	3	0	2	0
Continuous	3	4	3	0	2	1	1	1

Figures depict number of subjects

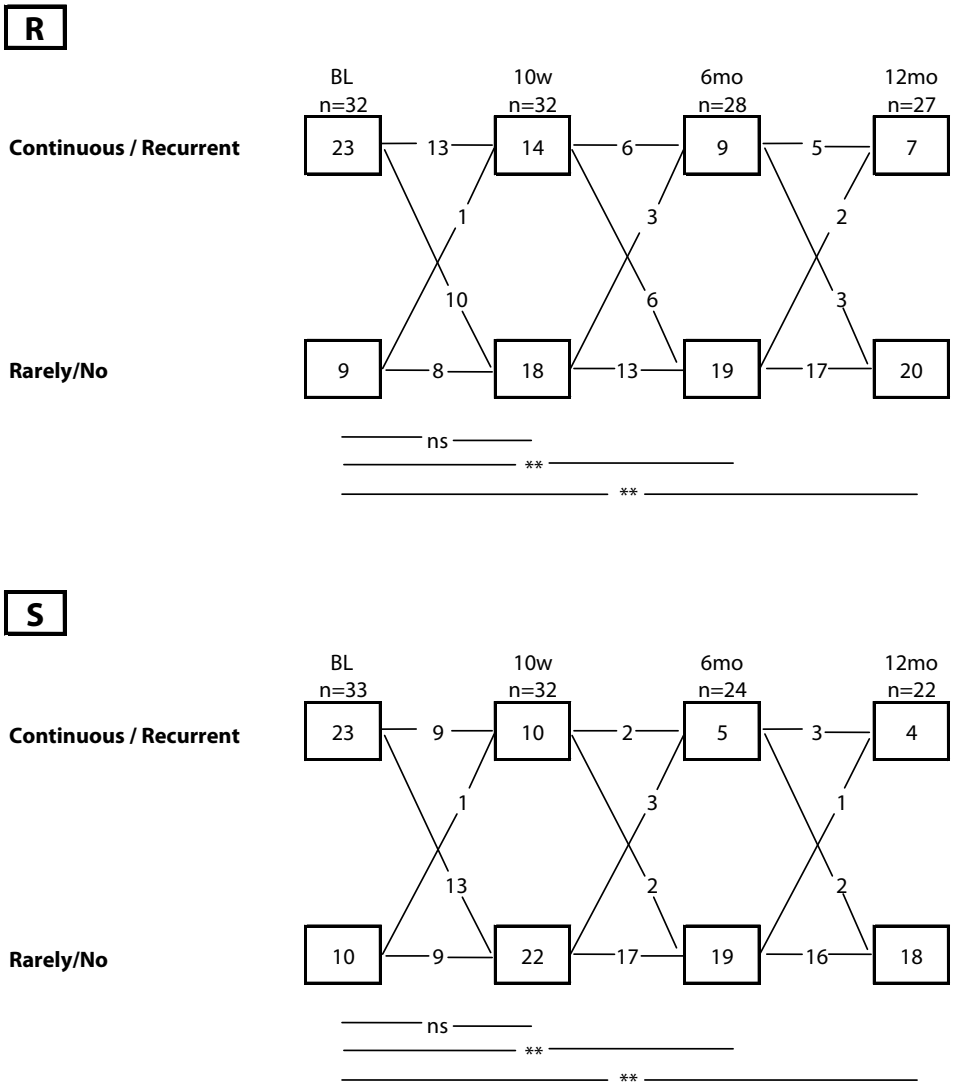


Figure 10. Fluctuation of Frequency of Headache at 10 weeks, and 6- and 12- month follow-ups.
R= prefabricated appliance; S= stabilization appliance
Figures depict number of subjects

Intensity of headache

At baseline, the mean intensity (NRS) of headache during the six months prior to the start of treatment was 5.3 in the R group and 6.1 in the S group. At the 12-month follow-up, the intensity had decreased to 2.1 in the R and 2.9 in the S group. The decrease was significant ($p<.001$) in both groups at every follow-up, without a significant difference between the groups (Table 10). At the 10 week follow-up, 58% of all patients reported a 30% reduction in intensity of headache, and 43% of the patients reported a 50% reduction in intensity of headache. The 12- month follow-up results showed percentages of 48% and 43%, respectively.

Table 10. Improvement of intensity of headache at 10 weeks, and at 6 and 12 months.
a) Reduction of intensity of headache according to a numeric rating scale (NRS)
b) Reduction of intensity of headache by 30% and 50%
NRS = numeric rating scale; R = prefabricated appliance; S = stabilization appliance

	Intensity of headache	B L		10 weeks		6 month		12 month		Significance level
		R	S	R	S	R	S	R	S	
a)	Reduction of intensity of headache (NRS)	(n=32)	(n=33)	(n=32)	(n=32)	(n=28)	(n=24)	(n=27)	(n=22)	
	NRS (mean)	5.3	6.1	3.0	3.2	2.7	2.2	2.1	2.9	NS
	SEM (+/-)	0.54	0.47	0.46	0.45	0.52	0.55	0.48	0.64	
b)	Reduction of intensity of headache (n)	(n=32)	(n=33)	(n=32)	(n=33)	(n=32)	(n=33)	(n=32)	(n=33)	
	30 % reduction of intensity			20	18	16	16	18	13	NS
	50 % reduction of intensity			14	14	14	14	16	12	NS

Chi-square test
There was no statisfically significant (NS) difference between groups R and s (≥ 05)
n = number of patients

Emotional functioning and headache

In a per protocol analysis, the NSPhS score was significantly associated with frequency of headache at baseline and at the 6-month follow-up (P≤ .05). A statistically significant association between frequency of headache and depression score at the 6-month (P≤ .05) and the 12-month follow-up was observed (P≤ .01).

6.4. Effect of appliance treatment of myogenous pain on salivary parameters (Study II)

Of all the 39 patients participating in the saliva study, 69% experienced general stress to some extent or very much. Especially work and education, as well as stress regarding general health showed high figures (58 and 59%, respectively). Thirty (77%) of the 39 patients used some kind of medication or vitamins. NSAIDs were most frequently used (n=15), followed by allergy/asthma medication (n=8), contraceptives (n=8), ulcer medication (n=4), and vitamins (n=4). Medication possibly affecting saliva flow (e.g. blood pressure medication) was used by only one patient.

After ten weeks´ treatment 36 (92%) of the 39 patients reported themselves to be better-much better-symptom-free regarding myofascial TMD pain, when measured on a 6-point rating scale. Two patients reported themselves to be completely symptom-free. Of the 39 patients, 30 (77%) reported a 30% reduction, and 26 (67%) a 50% reduction in worst pain.

6.4.1. Salivary cortisol

The cortisol values showed interindividual variations, depending on the time of sampling. The patients who had their samples collected before 10 am (early morning patients, n=20) showed a variation of 1.9 to 50 nmol/l. Only four subjects had values below 13.8. nmol/l (morning reference values 13.8. – 48.9 nmol/l) (Saliva Diagnostics 2006). Of the values representing samples collected after 10 am (n=19) only one could be considered high, 22 nmol/l, all other values were close to the given afternoon reference values of 1.4 – 8.6 nmol/l (Saliva Diagnostics 2006).

As for the association between stress and cortisol values we looked separately at cortisol afternoon values (n=19) which were certainly not influenced by the morning peak. At the first visit, no clear association between cortisol values and reported stress could be observed. When comparing the highest and lowest quartiles, two of the four subjects with the highest cortisol values reported general stress to some extent, while two reported very much general stress. Of the four subjects with the lowest cortisol values, three reported general stress to some extent, while one reported very little stress. Thus, no association between reported stress and cortisol values could be observed. The cortisol values of the S and R groups showed no between-groups differences at baseline or after treatment at the 6- and 10-week examinations and were thus pooled for the analyses of treatment effect.

In the analysis of the cortisol values of all subjects, no statistically significant changes were observed in intraindividual values after treatment when compared to before-treatment levels. No differences in cortisol levels were observed in subjects with a favourable compared to a less favourable treatment outcome, either when measured on a 6-point rating scale or when measured as a 30% and 50% reduction of worst pain. Not even the two patients who reported themselves to be totally symptom-free showed any changes in cortisol level during follow-up.

6.4.2. Salivary IgA and flow rate

The IgA values were within published reference values (Saliva Diagnostics 2006). IgA values measured at the first visit were not associated with reported stress levels. None of the patients showed hyposalivation values (<0.7 ml/min), while 37 of the 39 patients had flow rate values exceeding 1 ml/min.

At all but one visit (visit 1, $p<0.05$) the IgA mean values of the S and R groups showed no differences and were thus pooled for further analyses. There were no statistically significant differences in flow-rate values between the appliance groups; thus these data were also pooled. IgA and flow-rate levels remained intraindividually on a similar level throughout the study without statistically significant differences when baseline values were compared to after-treatment values. Nore were there any differences in these saliva variables in subjects with favourable versus less favourable treatment outcome either when measured on a verbal scale or when measured as a 30 or 50% reduction of worst pain.

7. DISCUSSION

The primary objective of this RCT was to evaluate the effectiveness of a prefabricated oral appliance compared with a stabilization appliance in the treatment of patients with TMD pain of myogenous origin, diagnosed according to the RDC/TMD, in the short as well as the long term. A secondary objective was to evaluate the effectiveness of these appliances, compared with each other, on frequency and intensity of headache in myofascial TMD pain patients with concomitant headache. Further, we wanted to evaluate the effect of appliance treatment on salivary stress-related parameters in these patients. The two treatment strategies used did not differ in magnitude or timing with regard to the four outcome domains, pain intensity, overall improvement, physical functioning, and emotional functioning, or in improvement in frequency and intensity of headache. No treatment- induced changes in saliva parameters could be registered.

7.1. Study design

The clinical use of occlusal appliances has been widespread clinically, although there has been much discussion in the literature concerning the true efficacy of appliance therapy. Somewhat diverging results were reached in recently published systematic reviews including RCTs on the efficacy of occlusal appliance therapy (Forssell and Kalso 2004, Türp et al. 2004, Al-Ani et al. 2005). Forssell and Kalso (2004) stated that the results did not justify drawing definite conclusions about the efficacy of splint therapy. The conclusion reached by Al-Ani and co-workers (2005) was similar. Türp and co- workers (2004) concluded that, based on the currently best available evidence, most patients with masticatory muscle pain will be helped by the use of a stabilization appliance. On the other hand, several studies have shown a better treatment outcome with a stabilization appliance compared to a control appliance that covers only the palate, both in the short and in the long term (Ekberg et al. 1998, 2003, Raphael and Marbach 2001, Ekberg and Nilner 2002, 2004). Therefore, the basis for our study set-up was that the stabilization appliance represents a “golden standard”, and is the most suitable appliance for conducting a comparative study. We did not include a control appliance or a group of patients receiving no appliance at all, because conducting a trial with a sample arm receiving only verbal counselling would be considered unethical according to the understanding of the Helsinki Declaration that lay people cannot be offered ineffective therapy for the sake of research purposes.

As the treatment of patients with myofascial TMD pain to a great extent takes place within primary care, it is important to know the results of different treatment modalities not only based on efficacy studies, but also on effectiveness studies. In a recent review by Fricton and co-workers (2010) on studies conducted during the period 1966 to March 2006, 44 RCTs were found, all of them efficacy studies, and the authors called for “studies assessing comparative effectiveness with other treatments in diverse clinical

settings". Effectiveness studies are important for the general practitioner because of their clinical relevance.

Recently, seven criteria for designing effectiveness studies were established and validated by the RTI-International (Research Triangle Institute, University of North Carolina Evidence-based Practice Center, Triangle Park, NC, USA)(Gartlehner et al. 2006). The authors attributed greater value to effectiveness studies than to efficacy studies, which is why the specificity of the process had to be high. That is, authors wanted to ensure that efficacy studies are not falsely rated as effectiveness studies. A cut-off of six criteria produced a specificity and sensitivity most suitable for this rationale. These criteria can provide a valid and simple tool to distinguish effectiveness studies from efficacy studies; for analysts, the applicability of systematic reviews can improve when emphasis is placed on the generalizability of the included studies, and the clinician can use the criteria to determine the external validity of individual studies given their particular populations of interest.

In the present study, the first criterion, "populations in primary care", was not fulfilled. For practical reasons, the patients were screened from referrals to the Department of Stomatognathic Physiology at either Malmö University or Turku University. We tried to compensate for this shortcoming by enrolling a general practitioner to perform all the treatments. The remaining six criteria were fulfilled in our study set-up: 2) less stringent inclusion criteria – in the present study: not rigorous, 3) health outcomes – in the present study: assessed with questionnaires, 4) long study duration – in the present study:12-month follow-up, 5) assessment of adverse effects – in the present study: changes in o0cclusion, control of vertical overbite, 6) adequate sample size to assess minimally important difference from a patient perspective – in the present study: sample size assessed according to a power analyses done before the on-set of our study, and 7) intention-to-treat analysis – in the present study: performed on reduction of myofascial TMD pain and headache. Thus, we consider the criteria for an effectiveness study to be fulfilled in our study set-up.

One strength of our study set-up was that we followed the recommendations by IMMPACT for evaluating treatment outcome. We also followed the guidelines of CONSORT for improving the quality of reports of parallel-group randomized trials (Moher et al. 2005). Additionally, all participating patients had the same diagnosis, i.e. TMD with myofascial pain, so the patient population was homogenous with regard to diagnosis. In some systematic reviews concerning appliance therapy (Forssell et. al 1998, Forssell and Kalso 2004, Al-Ani et al. 2005), patients with different diagnoses and different appliances were included, which makes the interpretation somewhat difficult.

A common problem in clinical long-term follow-ups is the number of drop-outs. This is a limitation of the present study as well. Out of 65 patients at baseline, 49 completed the study. The drop-out rate after one year was 23%; 16% in the R group and 33% in the S group. The reasons for the difference in drop-outs between the groups are only speculative: the large size of a stabilization appliance may sometimes affect the comfort,

and thereby the compliance of the patient (Ekberg and Nilner 2002, 2004). However, to compensate for eventual drop-outs we included more patients than the original power calculation indicated. In addition, despite the many drop-outs, analyses showed no difference regarding myofascial TMD pain, frequency and intensity of headache, and demographic data between the drop-outs and those who completed the study.

7.2. Overall improvement and reduction in pain intensity

Already at the 10-week follow-up, a positive result on primary outcome measures, i.e. overall improvement of subjective symptoms and reduction in pain intensity, was registered, without a statistically significant difference between the two appliance groups. The results remained essentially unchanged throughout the rest of the 12- month follow-up. These results are well in line with those of Ekberg and co-workers (2003) and Ekberg and Nilner (2004) on the use of a stabilization appliance in patients with myofascial TMD pain. In those studies, the stabilization appliance was compared to a non-occluding control appliance, and found to be superior. In the present study, both appliances, the stabilization appliance and the prefabricated appliance, included an occlusal coverage, which may be an important factor for the treatment outcome.

It should be borne in mind that increased cognitive awareness, regression to the mean, spontaneous remission, and natural fluctuation of the condition may be important factors for a positive treatment outcome, as well as the Hawthorne effect. Another important factor is the placebo effect, considered to occur in all active or real treatments. As soon as any kind of appliance is inserted intraorally, there will probably be an effect on the masticatory muscles (Greene and Laskin 1972). The information and counselling all patients received before appliance treatment probably also had an impact on treatment outcome (Dworkin et al. 1994).

7.3. Physical functioning

Graded Chronic Pain

A significant change to a lower grade of GCP was registered in both groups, compared to baseline, at all follow-ups. The level of GCP remained practically at the same level as at 10 weeks throughout the study. The overall change in GCP is in line with that found by Dworkin and co-workers (1994) when testing a brief, group cognitive-behavioural (CB) intervention delivered to the patients before usual treatment (UT, including occlusal appliance therapy) for temporomandibular disorders, compared to only UT after 3 and 12 months. Both groups showed improvement in characteristic pain and pain interference scores included in the GCP. It is also in line with a recent long-term follow-up by Truelove and co-workers (2006) using CPI. CPI was used to study the outcome of three different treatment modalities: dentist-prescribed self-care treatment, UT, UT plus a conventional flat-plane hard acrylic splint, and UT plus a soft vinyl splint. The average

CPI score decreased significantly during the one-year follow-up in all three groups. The authors concluded that neither splint therapy provided any greater benefit compared to self-care treatment alone. The self-care treatment included several modalities used in treating TMD (jaw relaxation, reduction of parafunctions, thermal packs, NSAIDs, passive opening stretches and suggestions about stress). Since combining several treatment methods has proven to be superior to single treatment modalities (De Boever et al. 2008), a similar result in all three groups was not surprising. In the present study, the overall outcome was successful with no differences between the groups, but we included no other treatment modalities except information and counselling.

Functional limitation of the masticatory system

The Jaw Functional Limitation Scale-20-Item version (JFLS-20) by Ohrbach and co-workers (2008) is an organ-specific instrument comprising three constructs for assessing the functional status of the masticatory system: mastication, jaw mobility, and verbal and emotional expression. The three scales exhibit properties that are ideal for both research and patient evaluation in patient groups with a range of functional limitations of the jaw (Ohrbach et al. 2008). We used the JFLS-20 because the three constructs included are conceptually distinct and empirically different from each other, making the system superior to other frequently used systems.

All three constructs included in the JFLS-20 showed a significant decrease, compared to baseline, in both groups, with no difference between the groups. Verbal and emotional expression did not decrease significantly before the 6-month follow-up, whereas the two other constructs did so already at the 10-week follow-up.

Physical functioning is one of two outcome domains recommended as core components of Health-Related Quality of Life that should be assessed in all clinical trials of treatments for chronic pain (Turk et al. 2003). In a systematic review on TMD and Oral Health-Related Quality of Life, by Dahlström and Carlsson (2010), all articles were found to describe a substantial impact on Oral Health-Related Quality of Life. The authors concluded that the reviewed studies convincingly demonstrated that Oral Health-Related Quality of Life was negatively affected among TMD patients.

7.4. Emotional functioning

Emotional functioning, including NSPhS and depression, is the second component of Health-Related Quality of Life recommended as a core outcome domain that should be assessed in all clinical trials of the efficacy and effectiveness of treatments for chronic pain (Turk et al. 2003).

NSPhS and depression

TMD patients have been reported to be more distressed than healthy individuals (Niemi et al. 1993). Several studies have reported on cognitive behaviour and depression and

NSPhS as important factors in the treatment outcome of TMD (Dworkin et al.1994, Rammelsberg et al. 2003, Turner et al. 2004). In the present study, the patients showed mainly moderate to severe baseline scores for NSPhS and depression, which corresponds well with other studies (Yap et al. 2002, Manfredini et al. 2009). We found a decrease in both scores at the 6- and 12-month follow-ups, and regarding depression, also at the 10-week follow-up in the R group. This result could be due to the TMD pain relief over time, as especially depression has been found to be related to pain perception (Slade et al. 2007, Baad-Hansen et al. 2008). Our results are in line with those of the above-mentioned study by Dworkin and co-workers (1994). The analyses showed that the measures of somatisation and depression improved over time in both groups.

7.5. Improvement in frequency and intensity of headache

Frequency and intensity of headache decreased both in the short and the long term in patients with myofascial TMD pain. Frequency of headache changed significantly in both groups from recurrent/continuous to no/rarely at both the 6- and the 12-month follow-up. This is well in line with the results by Ekberg and Nilner (2006) in patients with TMD of myogenous origin and concomitant TTH. They reported a reduction in the number of patients with headache at least once a week, and an improvement in headache in patients treated with a stabilization appliance.

Our results are in line with earlier reports focusing on the association between headache and TMD. Already in 1980, Magnusson and Carlsson (1980) found the prevalence of recurrent headaches in a group of TMD patients to be higher than in a group of dental patients. A reduction in the frequency of recurrent headache after TMD treatment was found. The authors concluded that patients consulting for recurrent headache should undergo functional examination of the masticatory system, and that headache patients with clinical signs of TMD should receive stomatognathic treatment. Forssell and co-workers (1985) compared patients suffering from migraine, muscle contraction and combination headache and TMD treated with occlusal adjustment to controls treated with mock adjustment, and concluded that “occlusal therapy can reduce both frequency and intensity in patients with muscle contraction and combination headache”. Shokker and co-workers (1990b) reported a significant decrease in both intensity and frequency of headache in 23 chronic headache patients also diagnosed with craniomandibular disorders and treated by a dentist. Another 25 patients were treated by a neurologist. The occlusal treatment included mainly stabilization splint therapy, and was reported to be superior when compared to the pharmacological treatment.

In a review by Svensson (2007), it was concluded that myofascial TMD and TTH disorders overlap and seem to share many of the same pathophysiological mechanisms. He suggested that orofacial pain and headache specialists should collaborate to improve the diagnostic techniques and management strategies of TMD and TTH. Also Ballegaard and co-workers (2008) reported recently on the overlap between primary headaches

and TMD. Their study included headache patients referred to a Headache Centre. The patients were diagnosed according to ICHD-II (2004) by neurologists. Sixty percent of the patients had more than one headache diagnosis; migraine was the most prevalent single diagnosis (15.2%), followed by TTH (11.1%). The patients were examined according to RDC/TMD, and a TMD diagnosis (Axis I) was identified in 56.1% of them. In a study by Shokker and co-workers (1990a), the results indicated that there is a close relationship between TMD and recurrent headache, irrespective of the neurological diagnosis of the headache. In our study, the main symptom of the patients was myofascial pain of myogenous origin, and 94% suffered concomitantly from headache. Although the headache diagnosis according to ICHD was not defined in our material, it is probable that the patients suffered mostly from TTH, and even more precisely from episodic TTH, since 28 patients out of 39 reporting recurrent headache had a headache frequency of less than 15 times a month and no one reported suffering from migraine or ongoing medication for migraine.

In our study, no consistent associations between frequency of headache and nonspecific physical symptoms and depression could be found. To our knowledge there is no other study reporting on these symptoms in association with headache in myofascial TMD pain patients in a long-term follow-up.

TMD patients have been reported to be more distressed than healthy individuals (Niemi et al. 1993). In a study by Ekberg and Nilner (2006) any kind of stressful life event seemed to influence the treatment outcome of headache at the 12-month follow-up. Using the same instrument in this study did not show any association between stressful life events and treatment outcome. The use of a validated questionnaire might have revealed some associations.

7.6. Additional outcomes

Pain on rest and movement

Pain on rest and movement of the mandible, criteria included in the RDC/TMD diagnosis, decreased significantly in both groups, without a significant difference between the groups, at all follow-ups. This is well in line with earlier studies on TMD patients with myofascial pain (Ekberg et al. 2003, Ekberg and Nilner 2004), treated with either a stabilization appliance or a control appliance, where the stabilization appliance was found to be superior.

PPT

We chose to use pressure algometry instead of manual palpation in assessing tenderness of masticatory muscles. Pressure algometry has been found to have acceptable intraobserver and interobserver reliability in quantifying tenderness to palpation (Jensen 1990). Visscher and co-workers (2004) concluded, using a logistic regression

analysis, that the recognition of TMD pain complaints based on pressure algometry was comparable to that of palpation. The assessments in this study were made with linearly increasing pressure and with duplicate recordings, which have been found to give a more reliable result than single recordings (Ohrbach and Gale 1989, Isseleé et al. 1997). The baseline values of PPT in the present study were comparable to those found in patients with local myalgia (Ernberg et al. 1999). The PPT values in the present study increased in the same way throughout the study, indicating similar improvements in both groups.

Ekberg and Nilner (2006) found in their study on treatment outcome of appliance therapy in patients with TMD of myogenous origin, that a 30% improvement in muscles tender to palpation was a factor which influenced a positive treatment outcome of TTH pain. In a material of 100 chronic headache patients referred to a neurologist, Shokker and co-workers (1990) found that 55 exhibited craniomandibular pain during examination of the stomatognathic system. They concluded that this suggested a possible relationship between headache and the condition of masticatory muscles. In spite of the fact that we found a significant increase in PPT in both groups, such a consistent connection was not found in our study. We registered the muscle tenderness in two muscles on both sides of the face using an algometer, whereas Ekberg and Nilner palpated five sites on each side of the face, which might explain the discrepancy between the results.

Mouth opening

There was only a mean difference of 2 mm between unassisted mouth opening at baseline and at the 12-month follow-up. Assisted mouth-opening showed no difference. Mouth-opening has been shown to be of little significance as an outcome measure for treatment of TMD, and this is well in line with the results of Ekberg and Nilner (2004) in TMD patients with myofascial pain.

Design of appliance and eventual adverse effects

Partial-covering appliances may be more likely to introduce changes in the occlusion compared with complete-coverage appliances (Clark et al. 2006). The present prefabricated appliance is a modification of the relaxation splint, which covers the teeth in the front and the palate, and is retained with clasps. The relaxation splint has long been in use by experienced clinicians in patients with myogenous TMD problems, to relax the masticatory muscles. The patients are advised to use the relaxation splint only at night-time because of the risk of appliance-induced malocclusion. In spite of the wide clinical use, there are no clinical trials on eventual adverse effects. Since the relaxation splint and the prefabricated appliance differ in their design, they are not directly comparable.

Another modification of the relaxation appliance, resembling the appliance in the present study, is the Dahl splint (Dahl et al. 1975), which has been thoroughly studied and used for a long time. The splint is an orthodontic/prosthetic appliance to be used day and night in patients with advanced localized attrition in the front. The appliance covers the upper front teeth, canine to canine, leaving the premolars and molars non-occluding,

aiming explicitly at an eruption in the premolar-molar area, thus providing space for prosthodontic reconstruction in the front. In evaluating the results, Dahl and Krogstad (1982, 1985) concluded that the action of the splint had been mainly one of allowing the posterior teeth erupt, even if the initial reaction was also one of intrusion of those teeth which carried the full load of the occlusal forces. A conclusive factor is certainly the time the appliance is worn. Dahl and co-workers stressed the importance of the splint being worn constantly, if changes in the occlusion were to be achieved. Our study was different in this respect; we pointed out clearly that the appliance was to be worn only at night-time to avoid changes in the occlusion.

We measured vertical overbite to assess possible adverse events, as proposed by both the guidelines of CONSORT (Moher et al. 2005) and the hallmarks for effectiveness studies by Gartlehner and co-workers (2006). For inter- and intra-individual reliability of the assessment of the vertical overbite we tested measurement errors in two different ways, according to the Dahlberg formula (Dahlberg 1948) and the intraclass coefficient (Shrout and Fleiss 1979), with practically no differences either between or within examiners.

At the 6-month follow-up, one patient in the R group with a vertical overbite of -1 mm at baseline, had an overbite of -3 mm. This patient was one of three patients in the R group with an open bite from 13-23 at the start of the study. The patient changed to a stabilization appliance and no further increase in vertical overbite could be registered at the 12-month follow-up. However, this could be a possible adverse event. To draw such a conclusion, a study including more patients is needed.

The Nociceptive Trigeminal Inhibition Tension Suppression System, NTI, was introduced by Shankland (2001). It is another type of frontal intraoral device, aiming mainly at reduction of TTH and migraine. Its specific design, with a single, pinpoint contact on the occluding element, is to supress the intensity of parafunctional pericranial muscular activity by taking advantage of the jaw-opening reflex. It has been strongly criticized (Magnusson et al. 2004), but later the conclusion from a review (Stapelmann and Türp 2008) was that evidence from RCTs suggest that the NTI may be successfully used for the management of bruxism and TMDs. However, there are risks of undesired effects, such as swallowing or aspiration of the device because of its small dimensions, the mobility of anterior teeth or occlusal changes, which is why the use of the NTI should be questioned. The size and the design of the present prefabricated appliance differ distinctly from those of the NTI, and thus exclude the risks of swallowing or aspiring it.

Use of occlusal appliances

In the present study, we advised the patients to use the appliances every night for the first 10 weeks and after this period when necessary. There was a difference in the frequency of use of the appliances, although this was not statistically significant. The R group used their appliances more frequently throughout the study. At the 12-month follow-up, 66% in the R group used their appliances several nights a week or more, while 50% in the S group did so. This result may indicate that the prefabricated appliance is more comfortable

to wear. Further, the majority of drop-outs were in the S group, which could be due to inadequate pain reduction or to patients experiencing the appliance as uncomfortable. The general practitioners in our effectiveness study found the prefabricated appliance to be easier to adjust compared to the stabilization appliance (personal communication). A periodical adjustment of the stabilization appliance is necessary to compensate for changes that may have caused pain, muscle activity, inflammation, or alterations in the structural relations of soft tissues (Okeson 2008). At the 10-week and 6-month follow-ups, it seemed that the need for adjustments was less for the prefabricated appliance, compared to the stabilization appliance, but at the 12-month follow-up, the need for adjustment was similar in both groups. No difference in the wear of the appliance surface was found. The wear was only slight in both groups throughout the study, indicating that none of the participants was a heavy night bruxer.

7.7. Salivary parameters: cortisol, IgA, flow-rate, stress

In this very first study dealing with cortisol, IgA and response of treatment of myofascial TMD pain with an occlusal appliance, the levels of the saliva parameters remained constant intraindividually throughout the study. No changes in salivary cortisol or IgA concentrations were observed despite the fact that the appliance treatment showed good treatment outcome regarding reduction of myofascial TMD pain. It is well known that cortisol values show a peak in the morning during the first hour after awakening. However, the samples of each individual were always taken at the same time of the day and thus each individual served as his/her own control. There were no changes when comparing the values before and after treatment, neither in the morning nor in the afternoon values.

In general, cortisol has been regarded as a “stress-hormone”. Studies on students exposed to experimental stress have shown some of the test persons having higher cortisol values and reacting with higher cortisol peaks compared to others (Kirschbaum et al. 1995). The same observation was made in a TMD patient material: some of the patients had starting values which were clearly higher than those of other patients and controls. Those with high values also reacted to the stress situation with much higher cortisol peaks than the hyposecretion group and the controls (Jones et al. 1997). However, comparing our results with the above studies is difficult, since we did not expose the patients to experimental stress but studied the cortisol levels as a function of treatment of TMD. Further, our subjects had been suffering from myofascial pain for an average of 65 months, although the majority of them had had pain for a shorter time (median 36 months). This situation is certainly different when compared to acute experimental stress. Adaptation might have occurred over time in our patients so successful treatment of myofascial TMD pain may therefore not have shown in salivary cortisol.

Previous studies have shown that TMD patients and subjects with a treatment need for TMD as well as subjects suffering from TMD and headache reported more stress

in general when compared to asymptomatic controls (Dworkin and LeResche 1992, Dworkin 1997, Kuttila et al. 1998, Niemi et al. 2006, Glaros et al. 2007). In a recent study (Nilsson and Dahlström 2010), patients with TMD appeared to be more psychologically distressed than controls evaluated psychometrically, but this stress was not reflected in awakening salivary cortisol levels. This is in accordance with our study where no association between reported high stress at baseline and cortisol levels could be found.

In accordance with the cortisol results, no association between IgA levels and high stress values could be observed at baseline. Previous studies have shown that stressful life events decrease salivary IgA (McClelland et al. 1985, Evans et al.1993). Various treatment interventions, for example, relaxation training and imagery directed at biological mechanisms, induced short-term increases in IgA levels (Jasnoski and Kugler 1987, Rider et al. 1990). However, one possible confounding factor may be saliva flow rate, which has not been taken into account in most of the previous studies. The results are therefore difficult to compare with each other and to interpret (Valdimarsdottir and Stone 1997). In our study saliva flow rate was taken into account.

All patients showed salivary flow rate values exceeding 0.7 ml/min, which has been regarded as a limit for hyposalivation. There were no treatment-induced changes in the flow rate values. This is contradictory to an earlier study, in which stimulated saliva flow rate showed a significant increase of 0.2-0.4 ml/min with a median of 0.2 ml/min in patients successfully treated for their TMD (Le Bell et al. 1985). However, the clinical relevance of an increase of 0.2 ml/min in the flow rate of stimulated saliva may be only marginal.

8. SUMMARY AND CONCLUSIONS

8.1. Summary

This RCT was carried out focusing especially on the effectiveness of a prefabricated occlusal appliance compared with the stabilization appliance in the treatment of myofascial TMD pain patients, as well as myofascial TMD pain patients with concomitant headache, both in a short and the long term. Additionally, the effect of appliance treatment on the stress-related salivary cortisol, as well as IgA and flow rate, were evaluated.

The study was carried out in collaboration with the Department of Stomatognathic Physiology at Malmö University, Sweden, during the period February 2005 to August 2007. Sixty-six adult patients, all with the diagnosis of myofascial TMD pain, and 94% with concomitant headache, were included in the study. Thirty-two patients were treated in Malmö and 33 in Turku, half of them with the prefabricated appliance, and the other half with a stabilization appliance. Patients were examined according to Research Diagnostic Criteria for TMD. They were randomly assigned to either treatment group, and history questionnaires and clinical examinations were performed at baseline, at 6 and 10 weeks, and at 6- and 12- month follow-ups. Thirty-nine patients participated in the saliva study and salivary analyses were performed at baseline, and at 6 and 10 weeks.

Treatment outcome was evaluated for pain intensity, overall improvement, physical and emotional functioning, the four chronic pain outcome domains initiated by IMMPACT. Improvement in headache was evaluated for frequency and intensity of headache.

There were no differences between the groups at baseline. The primary outcome domains, pain intensity and overall improvement, showed a positive treatment outcome already at the 10-week follow-up, with the results remaining essentially at the same level throughout the study. Physical functioning, consisting of GCP and functional limitation of the masticatory system, showed the same pattern. Verbal and emotional expression was an exception: there was no significant decrease before the 6-month follow-up. Emotional functioning, both NSPhS and depression scores, decreased at the 6- and 12-month follow-ups. There was no statistical difference between the two appliance groups throughout the study.

Improvement in frequency and intensity of headache showed the same pattern with a significant positive treatment outcome at the 10-week follow-up. These results also remained unchanged throughout the study. Furthermore, there was no statistically significant difference between the two appliances at follow-ups. In our study, no consistent associations between frequency of headache and non-specific physical symptoms and depression could be found. To our knowledge there is no other study reporting on these symptoms in association with headache in myofascial TMD pain patients in a long-term follow-up.

This is the very first study dealing with cortisol, IgA and response to treatment of myofascial TMD pain with an occlusal appliance. No changes in salivary cortisol or IgA concentrations were observed despite the fact that the appliance treatment showed good treatment outcome regarding reduction of myofascial TMD pain.

The results of the present study indicate, taking into consideration all the separate treatment outcomes, that the prefabricated occlusal appliance seems to be as effective as the stabilization appliance in the treatment of TMD pain of a myogenous origin, as well as concomitant headache, in both the short and the long term.

In the present RCT, we focused on patients diagnosed with TMD pain of a myogenous origin. Thus, there is a need for further research on the effectiveness of the prefabricated appliance in patients with TMD pain of an arthrogenous origin. From a clinical point of view, it would also be of interest and importance to study eventual adverse effects of the prefabricated appliance in a randomized controlled trial with a sufficient number of patients and various types of occlusion. Such a study would, however, require more patients than were included in the present study.

8.2. Conclusions

The prefabricated occlusal appliance seems to be a convenient means of providing a patient with myofascial TMD pain with an occlusal appliance. A single clinical visit is required and there are no laboratory costs.

On the basis of the results, the following conclusions can be drawn:

- The effectiveness of the prefabricated appliance seems to be similar to that of the stabilization appliance in alleviating myofascial pain in TMD patients, both in the short and the long term.
- The short- and long-term effectiveness of the prefabricated appliance in reducing headache frequency and intensity in patients with myofascial TMD pain seems to be similar to that of the stabilization appliance.
- Salivary cortisol and IgA levels are not influenced by occlusal appliance therapy in patients with myofascial TMD pain.

It therefore seems justifiable to recommend the use of this prefabricated occlusal appliance for the treatment of patients with myofascial TMD pain and headache, in both the short and the long term.

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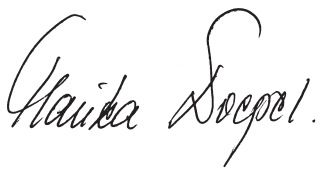

10. REFERENCES

Agerberg G, Inkapööl I. Craniomandibular disorders in urban Swedish population. J Craniomandib Disord Oral Pain 1990;4:154-164.

Al-Ani MZ, Davies SJ, Gray RJM, Sloan P, Glenny AM. Stabilisation splint therapy for temporomandibular pain dysfunction syndrome (Review). Cochrane Database Syst Rev 2004;1:CD002778.

Al-Jundi MA, John MT, Setz JM, Szentpetery A, Kuss O. Meta-analysis of treatment need for temporomandibular disorders in adult nonpatients. J Orofac Pain 2008;22:97-107.

Anderson GC, Gonzales YM, Ohrbach R, Truelove EL, Sommers E, Look JO, Shiffman EL. The Research Diagnostic Criteria for Temporomandibular Disorders. VI: future directions. J Orofac Pain 2010;24:79-88.

Baad-Hansen L, Leijon G, Svensson P, List T. Comparison of clinical findings and psychosocial factors in patients with atypical odontalgia and temporomandibular disorders. J Orofac Pain 2008;22:7-14.

Ballegaard V, Thede-Schmidt-Hansen P, Svensson P, Jensen R. Are headache and temporomandibular disorders related? A blinded study. Cephalalgia 2008;28:721-727 .

Barbosa Tde S, Miyakoda LS, Pocztaruk Rde L, Rocha CP, Gaviao MB. Temporomandibular disorders and bruxism in childhood and adolescence: review of literature. Int Pediatr Otothinolaryngol 2008;72:299-314.

Carlson CR, Bertrand PM, Ehrlich AD, Maxwell AW, Burton RG. Physical self-regulation training for the management of temporomandibular disorders. J Orofac Pain 2001;15:47-55.

Carlsson GE. Epidemiology and treatment need for temporomandibular disorders. J Orofac Pain 1999;13:232-237.

Carlsson GE, Egermark I, Magnusson T. Predictors of signs and symptoms of temporomandibular disorders: A 20-year follow-up study from childhood to adulthood. Acta Odontol Scand 2002;60:180-185.

Carlsson GE, Magnusson T, Egermark I. Prediction of demand for treatment of temporomandibular disorders based on a 20-year follow-up study. J Oral Rehabil 2004;31(6):511-517.

Christidis N, Kopp S, Ernberg M. The effect of mechanical pain threshold over human muscles by oral administration of granisetron and diclofenac-sodium. Pain 2005;113:265-270.

Ciancaglini R, Gherlone EF, Radaelli G. Association between loss of of occlusal support and symptoms of functional disturbances of the masticatory system. J Oral Rehabil 1999;26:248-253.

Ciancaglini R, Gherlone EF, Radaelli G. Unilateral temporomandibular disorder and asymmetry of occlusal contacts. J Prosthet Dent 2003;89:180-185.

Clark GT, Minakuchi H. Oral appliances. In: TMDs, an evidence-based approach to diagnosis and treatment. Laskin DM, Greene CS, Hylander WL (eds). Chicago: Quintessence, 2006:377-390.

Crider AB, Glaros AG. A meta-analysis of EMG biofeedback treatment of temporomandibular disorders. J Orofac Pain 1999;13:29-37.

Dahl BL, Krogstad O, Karlsen K. An alternative treatment in cases with advanced localized attrition. J Oral Rehabil 1975;2:209-214.

Dahl BL, Krogstad O. The effect of a partial bite raising splint on the occlusal face height. An X-ray cephalometric study in human adults. Acta Odontol Scand 1982;40:17-24.

Dahl BL, Krogstad O. Long-term observations of an increased occlusal face height obtained by a combined orthodontic/prosthetic approach. J Oral Rehabil 1985;12:173-176.

Dahlberg G. Statistical Methods for medical and biological students. London, United Kingdom: Allen and Unwin 1948.

Dahlström L, Carlsson GE. Temporomandibular disorders and oral health-related quality of life. A systematic review. Acta Odontol Scand 2010;68:80-85.

Dahlström L, Haraldson T. Bite plates and stabilization splints in mandibular dysfunction. A clinical and electromyographic comparison. Acta Odontol Scand 1985;43:109-114.

Dahlström L, Haraldsen T. Immediate electromyographic response in masseter and temporal muscles to bite plates and stabilization splints. Scand J Dent Res 1989;97:533-538.

Da Silva Andrade A, Gamero GH, Pereira LJ, Junqueira Zanin IC, Gaviao MB. Salivary cortisol levels in young adults with temporomandibular disorders. Minerva Stomatol 2008;57:109-116.

Dao TT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP. The efficacy of oral splints in the treatment of myofascial pain in the jaw muscles: a controlled clinical trial. Pain 1994;56:85-94.

Dao TT, LeResche L. Gender differences in pain. J Orofac Pain 2000;14:169-184;discussion 184-195.

De Boever JA, Carlsson GE. Etiology and differential diagnosis. In: Temporomandibular joint and masticatory muscle disorders. Zarb GA, Carlsson GE, Sessle BJ, Mohl ND (eds). Copenhagen: Munksgaard 1994, pp. 171-187.

De Boever JA, Carlsson GE, Klineberg IJ. Need for occlusal therapy and prosthodontic treatment in the management of temporomandibular disorders. Part I. Occlusal interferences and occlusal adjustment. J Oral Rehabil 2000a;27:367-379.

De Boever JA, Carlsson GE, Klineberg IJ. Need for occlusal therapy and prosthodontic treatment in the management of temporomandibular disorders. Part II. Tooth loss and prosthodontic treatment. J Oral Rehabil 2000b;27:647-659.

De Boever JA, Nilner M, Orthlieb J-D, Steenks MH. Recommendations by the EACD for Examination, Diagnosis, and Management of Patients with Temporomandibular Disorders and Orofacial Pain by the General Dental Practitioner. J Orofac Pain 2008;3:268-278.

De Kanter RJAM, Truin GJ, Burgersdijk RCW, Van´t Hof MA, Battistuzzi PGFCM, Kalsbeck H, Käyser AF. Prevalence in the Dutch adult population and a meta-analysis of signs and symptoms of temporomandibular disorders. J Dent Res 1993;72:1509-1518.

De Laat A, Stappaerts K, Papy S. Counseling and physical therapy as treatment for myofascial pain of the masticatory system. J Orofac Pain 2003;17:42-49.

De Leeuw JRJ, Steenks MH, Ros WJG, Lobbezoo-Scholte AM, Bosman F, Winnubst JAM. Assessment of treatment outcome in patients with craniomandibular dysfunction. J Oral Rehabil 1994;21:655-666.

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS, Maixner W. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135-143.

Dworkin RH, Turk DC, Wyrwich K, Beaton D, Cleeland CS, Farrar J, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. Pain 2008;9:105-121.

Dworkin SF. Behavioral and educational modalities. Oral Surg Oral Med Oral Pathol 1997;83:128-133.

Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Dis 1992;6:300-354.

Dworkin SF, LeResche L, DeRouen T, Von Korff M. Assessing clinical signs of temporomandibular disorders: reliability of clinical examiners. J Prosthet Dent 1990;63:574-579.

Dworkin SF, Sherman J, Mancl L, Ohrbach R, LeResche L, Truelove E. Reliability, Validity, and Clinical Utility of the Research Diagnostic Criteria for Temporomandibular Disorders Axis II Scales: Depression, Non-Specific Physical Symptoms, and Graded Chronic Pain. J Orofac Pain 2002;3:207-220.

Dworkin SF, Turner JA, Wilson L, Massoth D, Whitney C, Huggins KH, Burgess J, Sommers E,Truelove E. Brief group cognitive-behavioral intervention for temporomandibular disorders. Pain 1994;59:175-187.

Egermark I, Carlsson GE, Magnusson T. A 20-year longitudinal study of subjective symptoms of temporomandibular disorders from childhood to adulthood. Acta Odontol Scand 2001;59:40-48.

Egermark I, Magnusson T, Carlsson GE. A 20-year follow-up of signs and symptoms of temporomandibular disorders and malocclusion in subjects with and without orthodontic treatment in childhood. Angle Orthod 2003;73:109-115.

Ekberg EC, Nilner M. A 6- and 12-month follow-up of appliance therapy in TMD patients: a follow-up of a controlled trial. Int J Prosth 2002;15:564-570.

Ekberg EC, Nilner M. Treatment outcome of appliance therapy in temporomandibular disorder patients with myofascial pain after 6 and 12 months. Acta Odontol Scand 2004;62:343-349.

Ekberg EC, Nilner M. Treatment outcome of short- and long-term appliance therapy in patients with TMD of myogenous origin and tension-type headache. J Oral Rehab 2006;33:713-721.

Ekberg EC, Vallon D, Nilner M. Occlusal appliance therapy in patients with temporomandibular disorders. A double-blind controlled study in a short-term perspective. Acta Odontol Scand 1998;56:122-128.

Ekberg EC, Vallon D, Nilner M. Treatment outcome of headache after occlusal appliance therapy in a randomised controlled trial among patients with temporomandibular disorders of mainly arthrogenous origin. Swed Dent J 2002;26:115-124.

Ekberg EC, Vallon D, Nilner M. The efficacy of appliance therapy in patients with temporomandibular disorders of mainly myogenous origin. A randomized, controlled, short-term trial. J Orofac Pain 2003;17:133-139.

Eriksson PO, Häggman-Henrikson B, Zafar H. Jaw-neck dysfunction in whiplash-associated disorders. Arch Oral Biol 2007;52:404-408.

Ernberg H, Hedenberg-Magnusson B, Alstergren P, Lundeberg T, Kopp S. Pain, allodynia, and serum serotonin level in orofacial pain of muscular origin. J Orofac Pain 1999;13:56-62.

Ernberg M, Lundeberg T, Kopp S. Effect of propranolol and granisetron on experimentally induced pain and allodynia/hyperalgesia by intramuscular injection of serotonin into the human masseter muscle. Pain 2000;85:339-346.

Ernst E, White AR. Acupuncture as a treatment for temporomandibular joint dysfunction: a systematic review of randomized trials. Arch Otolaryngol Head Neck Surg 1999;125:269-272.

Evans P, Bristow M, Hucklebridge F, Clow A, Walters N. The relationship between secretory immunity, mood and life-events. Br J Clin Psychol 1993; 32: 227-236.

Evaskus DS, Laskin DM. A biochemical measure of stress in patients with myofascial pain-dysfunction syndrome. J Dent Res 1972;51:1464-1466.

Eversole LR, Stone CE, Matheson D, Kaplan H. Psychometric profiles and facial pain. Oral Surg Oral Med Oral Pathol 1985;60:269-274.

Farrar J, Young Jr J, LaMoreaux L, Werth J, Poole RM. Clinical importance of changes in a chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-158.

Forssell H, Kalso E. Application of Principles of Evidence-Based-Medicine to Occlusal Treatment of Temporomandibular Disorders: Are There Lessons to be Learned? J Orofac Pain 2004;18:9-22.

Forssell H, Kalso E, Koskela P, Vehmanen R, Puukka P, Alanen P. Occlusal treatments in temporomandibular disorders: a qualitative systematic review of randomized controlled trials. Pain 1999;83:549-560.

Forssell H, Kirveskari P, Kangasniemi P. Changes in headache after treatment of mandibular dysfunction. Cephalalgia 1985;5:229-236.

Fricton J, Look JO, Wright E, Alencar FGP Jr, Chen H, Lang M, Oyuang W, Velly AM. Systematic Review and Meta-analysis of Randomized Controlled Trials Evaluating Intraoral Orthopedic Appliances for Temporomandibular Disorders. J Orofac Pain 2010;3:237-254.

Galli U, Gaab J, Ettlin DA, Ruggia F, Ehlert U, Palla S. Enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal axis in chronic myogenous facial pain. Eur J Pain 2009;13:600-605.

Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. Criteria for Distinguishing Effectiveness From Efficacy Trials in Systematic Reviews. Technical Review 12 (Prepared by the RTI-International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) AHRQ Publication No. 06-0046. Rockville, MD: Agency for Healthcare Research and Quality. April 2006.

Gelb H, Tarte J. A two year clinical dental evaluation of 200 cases of chronic headache: the craniocervical-mandibular syndrome. J Am Dent Assoc 1975;91:1230-1236.

Gesch D, Bernhard O, Alte D, Kocher T, John U, Hensel E. Malocclusions and clinical signs or subjective symptoms of temporomandibular disorders (TMD) in adults. Results of the population-based Study of Health in Pomerania (SHIP). J Orofac Orthop 2004;65:88-103.

Glaros AG, Urban D, Locke J. Headache and temporomandibular disorders: evidence for diagnostic and behavioural overlap. Cephalalgia 2007;27:542-549.

Goddard G, Karibe H, McNeill C, Villafuerte E. Acupuncture and sham acupuncture reduce muscle pain in myofascial pain patients. J Orofac Pain 2002;16:71-76.

Godwin M, Ruhland L, Casson I, McDonald S, Delva D, Birtwhistle R, Lam M, Seguin R. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003;3:28.

Green CS, Laskin DM. Splint therapy for the myofascial pain-dysfunction (MPD) syndrome: a comparative study. J Am Dent Assoc 1972;84:624-628.

Grönqvist J, Häggman-Henrikson B, Eriksson PO. Impaired jaw function and eating difficulties in whiplash-associated disorders. Swed Dent J 2008;32:171-177.

Helkimo M. Studies on function and dysfunction of the masticatory system. I. An epidemiological investigation of symptoms of dysfunction in Lapps in the north of Finland. Proc Finn Dent Soc 1974;70:37-49.

Hidaka O, Yanagi M, Takada K. Mental stress-induced physiological changes in the human masseter muscle. J Det Res 2004;83:227-231.

Hirsch C, John MT, Stang A. Association between generalized joint hypermobility and signs and diagnoses of temporomandibular disorders. Eur J Oral Sci 2008;116:525-530.

Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT. Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284-288.

Isseleé H, De Laat A, Lesaffre E, Lysens R. Short-term reproducibility of pressure pain thresholds in masseter and temporalis muscles of symptom-free subjects. Eur J Oral Sci 1997;105:583-587.

Jasnoski M, Kugler J. Relaxation, imagery and neuroimmunomodulation. Annals New York Academy of Sciences 1987; 722-730.

Jensen K. Quantification of tenderness by palpation and use of pressure algometers. In: Fricton JR, Awad E (eds). Advances in Pain Research and Therapy, vol 17:Myofascial pain and fibromyalgia. New York: Raven Press, 1990:165-181.

Jensen R, Rasmussen BK, Pedersen B, Olesen J. Muscle tenderness and pressure pain thresholds in headache. A population study. Pain 1993a;52:193-199.

Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J. Prevalence of oromandibular dysfunction in a general population. J Orofac Pain 1993b;7:175-182.

Johansson A, Unell L, Carlsson GE, Söderfeldt B, Halling A. Gender difference in symptoms related to temporomandibular disorders in a population of 50-year-old subjects. J Orofac Pain 2003;17:29-35.

Johansson A, Unell L, Carlsson GE, Söderfeldt B, Halling A. Associations between social and general health factors and symptoms related to temporomandibular disorders and bruxism in a population of 50-year-old subjects. Acta Odontol Scand 2004;62:231-237.

Johansson A, Unell L, Carlsson GE, Söderfeldt B, Halling A. Differences in four reported symptoms related to temporomandibular disorders in a cohort of 50-yaer-old subjects followed up after 10 years. Acta Odontol Scand 2008;66:50-57.

Johansson A, Wenneberg B, Wagersten C, Haraldson T. Acupuncture in treatment of facial muscular pain. Acta Odontol Scand 1991;49:153-158.

John MT, Dworkin SF, Mancl LA. Reliability of temporomandibular disorder diagnoses. Pain 2005;118:61-69.

Jokstad A. The NTI-tss device may be used successfully in the management of bruxism and TMD. Evid Based Dent 2009;10:23.

Jones DA, Rollman GB, Brooke RI. The cortisol response to psychological stress in temporomandibular dysfunction. Pain 1997;72:171-182.

Karppinen K, Eklund S, Suominen E, Eskelin M, Kirveskari P. Adjustment of dental occlusion in treatment of chronic cervicobrachial pain and headache. J Oral Rehabil 1999;26:715-721

Kim MR, Graber TM, Viana MA. Othodontics and temporomandibular disorder: A meta-analysis. Am J Orthod Dentofacial Orthop 2002;121:438-446.

Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments ad applications. Psychoneuroendocrinology 1994;4:313-333.

Kirschbaum C, Prussner JC, Stone AA, Federenko I, Gaab J, Lintz D, Schommer N, Hellhammer DH. Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. Psychosom Med 1995;57:468-474.

Kirveskari P, Alanen P, Jämsä T. Association between craniomandibular disorders and occlusal interferences. J Prosthet Dent 1989a;62:66-69.

Kirveskari P, Le Bell Y, Salonen M, Forssell H, Grans L. Effect of elimination of occlusal interferences on signs and symptoms of craniomandibular disorders in young adults. J Oral Rehabil 1989b;16:21-26.

Kirveskari P, Jämsä T, Alanen P. Occlusal adjustment and the incidence of demand for temporomandibular disorder treatment. J Prosthet Dent 1998;79:433-438.

Koh H, Robinson PG. Occlusal adjustment for treating and preventing temporomandibular joint disorders (Review). Cochrane Database Syst Rev 2003;1:CD003812.

Korszun A, Young EA, Singer K, Carlson NE, Brown MB, Crofford L. Basal circadian cortisol secretion in women with temporomandibular disorders. J Dent Res 2002;81:279-283.

Kreiner M, Betancor E, Clark GT. Occlusal stabilization appliance-evidence of their efficacy. J Am Dent Assoc 2001; 132:770-777.

Kuttila M, Kuttila S, Le Bell Y, Alanen P. Fluctuation of treatment need for temporomandibular disorders and age, gender, stress, and diagnostic subgroup. Acta Odontol Scand 1997a;55:350-355.

Kuttila M, Kuttila S, Le Bell Y, Alanen P. Association between TMD treatment need, sick leaves and use

of health care services for adults. J Orofacial Pain 1997b;11:242-248.

Kuttila M, Niemi PM, Kuttila S, Alanen P, Le Bell Y. TMD treatment need in relation to age, gender, stress and diagnostic subgroup. J Orofacial Pain 1998;12:67-74.

Könönen M, Nyström M. A longitudinal study of craniomandibular disorders in Finnish adolescents. J Orofac Pain 1993;7:329-336.

Laskin DM, Greene CS, Hylander WL. TMD`s: An Evidence-Based Approach to Diagnosis and Treatment. Chicago: Quintessence 2006.

Le Bell Y, Jämsä T, Korri S, Niemi P, Alanen P. Effect of artificial occlusal interferences depends on previous experience of temporomandibular disorders. Acta Odontol Scand 2002;60:219-222.

Le Bell Y, Niemi P, Jämsä T, Kylmala M, Alanen P. Subjective reactions to intervention with artificial interferences in subjects with and without a history of temporomandibular disorders. Acta Odontol Scand 2006;64:59-63.

Le Bell Y, Söderling E, Kirveskari P, Alanen P. Flow-rate, pH and buffer capacity of whole saliva before and after treatment of TMJ dysfunction. Proc Finn Dent Soc 1985;81:226-229.

LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 1997;8:291-305.

LeResche L. Epidemiology of orofacial pain. In: Lund JP, Lavigne GJ, Dubner R, Sessle B (eds). Orofacial Pain: From Basic Science to Clinical Management. The Transfer of Knowledge in Pain Research to Education. Chicago: Quintessence, 2001:15-25.

LeResche L, Mancl LA, Drangsholt MT, Saunders K, Korff MV. Relationship of pain and symptoms to pubertal development in adolescents. Pain 2005;118:201-209.

Lehtonen OP, Gråhn E, Ståhlberg T, Laitinen LA. Amount and avidity of salivary and serum antibodies against Streptococcus mutans in two groups of human subjects with different dental caries susceptibility. Infect Immun 1984;43:308-313.

Liljeström M-R, Jämsä T, Le Bell Y, Alanen P, Anttila P, Metsähonkala L, Aromaa M, Sillanpää M. Signs and symptoms of temporomandibular disorders in children with different types of headache. Acta Odontol Scand 2001;59:413-417.

Lindfors E, Magnusson T, Tegelberg Å. Treatment with interocclusal appliances. Swed Dent J 2006;30:123-134.

Lindroth JE, Schmidt JE, Carlson CR. A comparison between masticatory muscle pain patients and intracapsular pain patients on behavioral and psychosocial domains. J Orofac Pain 2002;16:277-283.

Lipton JA, Ship J, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124:115-121.

List T, Axelsson S, Leijon G. Pharmacologic interventions in the treatment of temporomandibular disorders, atypical facial pain, and burning mouth syndrome. A qualitative systematic review. J Orofac Pain 2003;17:301-310.

List T, Helkimo M. Acupuncture and occlusal splint therapy in the treatment of craniomandibular disorders. II. A 1-year follow-up study. Acta Odontol Scand 1992;50:375-385.

List T, Wahlund K, Wenneberg B, Dworkin SF. TMD in children and adolescents: prevalence of age, gender differences, and perceived treatment need. J Orofac Pain 1999;13:9-20.

Lobbezoo F, Lavigne GJ. Do bruxism and temporomandibular disorders have a cause-and-effect relationship? J Orofac Pain 1997;11:15-23.

Look JO, John MT, Tai F, Huggins KH, Lenton PA, Truelove EL, Ohrbach R, Andersson GC, Shiffman EL. The Research Diagnostic Criteria for Temporomandibular Disorders. II: reliability of Axis I diagnoses and selected clinical measures. J Orofac Pain 2010;24:25-34.

Magnusson T, Adiels AM, Nilsson HL, Helkimo M. Treatment effect on signs and symptoms of temporomandibular disorders – Comparison between stabilization splint and a new type of splint (NTI). A pilot study. Swed Dent J 2004;28:11-20.

Magnusson T, Carlsson GE. Comparison between two groups of patients in respect of headache and mandibular dysfunction. Swed Dent J 1978a;2:85-92.

Magnusson T, Carlsson GE. Recurrent headaches in relation to temporomandibular joint pain-dysfunction. Acta Odontol Scand 1978b;36:333-338.

Magnusson T, Carlsson GE. Changes in recurrent headache and mandibular dysfunction after various types of dental treatment. Acta Odontol Scand 1980;38:311-320.

Magnusson T, Carlsson GE. A 2,5 year follow-up of changes in headache and mandibular dysfunction after stomatognathic treatment. J Prosthet Dent 1983;49:398-402.

Magnusson T, Carlsson GE, Egermark-Eriksson I. An evaluation of the need and demand for treatment of craniomandibular disorders in a young Swedish population. J Craniomandib Disord Facial Oral Pain 1991;5:57-63.

Magnusson T, Carlsson GE, Egermark I. Changes in clinical signs of craniomandibular disorders from the age of 15 to 25 years. J Orofacial Pain 1994;8:207-215.

Magnusson T, Egermark I, Carlsson EG. A prospective investigation over two decades on signs and symptoms of temporomandibular disorders and associated variables. A final summary. Acta Odontol Scand 2005;63:99-109.

Manfredini D, Bandettini di Poggio A, Cantini E, Dell´Osso L, Bosco M. Mood and anxiety psychopathology and temporomandibular disorders: a spectrum approach. J Oral Rehabil 2004;31:933-940.

Manfredini D, Landi N, Bandettini Di Poggio A, Dell´Osso L, Bosco M. A critical review on the importance on psychological factors in temporomandibular disorders. Minerva Stomatol 2003;52:321-330.

Marklund S, Wänman A. Risk factors associated with incidence and persistence of signs and symptoms of temporomandibular disorders. Acta Odontol Scand 2010;68:289-299.

McClelland DC, Ross G, Patel V. The effect of an academic examination on salivary norepinephrine and immunoglobulin levels. J Human Stress 1985;11: 55-59.

McCreary CP, Clark GT, Merril RL, Flack V, Oakley ME. Psychological distress and diagnostic subgroups of temporomandibular disorder patiets. Pain 1991;44:29-34.

McNeely ML, Armijo Olivo S, Magee DJ. A systematic review of the effectiveness of physical therapy interventions for temporomandibular disorders. Phys Ther 2006;86:710-725.

McNeill C (ed). Introduction. In: Temporomandibular disorders: Guidelines for classification, assessment, and management. Quintessence, Chicago, 1993:11-18.

Medlicott MS, Harris RS. A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. Phys Ther 2006;86:955-973.

Michelotti A, Steenks MH, Farella M, Parisini F, Cimino R, Martina R. The additional value of a home physical therapy regimen versus patient education only for the treatment of myofascial pain of the jaw muscles: short-term results of a randomized clinical trial. J Orofac Pain 2004;18:114-125.

Michelotti A, de Wijer A, Steenks M, Farella M. Home-exercise regimes for the management of non-specific temporomandibular disorders. J Oral Rehabil 2005;32:779-785.

Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. Explore (NY) 2005;1:40-45.

Mohlin B, Ingervall B, Thilander B. Relation between malocclusion and mandibular dysfunction in Swedish men. Eur J Orthod 1980;2:229-238.

Mohlin B, Kurol J. To what extent do deviations from an ideal occlusion constitute a health risk? Swed Dent J 2003;27:1-10.

Naeije M, Kalaykova S, Visscher CM, Lobbezoo F. Evaluation of the Research Diagnostic Criteria for Temporomandibular Disorders for the recognition of an anterior disc displacement with reduction. J Orofac Pain 2009;4:303-311.

Niemi P, Le Bell Y, Koskinen-Moffet L. Self-reported symptoms of stress in Finnish patients with craniomandibular disorders. J Orofacial Pain 1993;70:158-164.

Niemi P, Le Bell Y, Kylmälä M, Jämsä T, Alanen P. Psychological factors and responses to to artificial enterferences in subjects with and without a history of temporomandibular disorders. Acta Odontol Scand 2006;64:300-305.

Nilner M. Epidemiologic studies in TMD. In: McNeill C. Current controversies in temporomandibular disorders. Quintessence, Carol Stream, 1992:21-26.

Nilner M. Critical Commentary 3: Application of principles of evidence-based medicine to occlusal treatments for temporomandibular disorders: are there lessons to be learned? J Orofac Pain 2004;18:27-30.

Nilsson AM, Dahlström L. Perceived symptoms of psychological distress and salivary cortisol levels in young women with muscular or disk-related temporomandibular disorders. Acta Odontol Scand 2010;68:284-288.

Nilsson H. Resilient Appliance Therapy of Temporomandibular Disorders. Thesis 2010.

Nilsson H, Limchaichana N, Nilner M, Ekberg EC. Short-term treatment of a resilient appliance in TMD pain patients: a randomized controlled trial. J Oral Rehabil 2009;36:547-555.

Nilsson IM, List T, Drangsholt M. Prevalence of temporomandibular pain and subsequent dental treatment in Swedish adolescents. J Orofac Pain 2005;19:144-150

Ohrbach R, Gale EN. Pressure pain thresholds in normal muscles: Reliability, measurement effects and topographic differences. Pain 1989;37:257-263.

Ohrbach R, Larsson P, List T. The Jaw Functional Limitation Scale: Development, Reliability, and Validity of 8-Item and 20-Item Versions. J Orofac Pain 2008;22:219-230.

Ohrbach R, Turner JA, Sherman JJ, Mancl LA, Truelove EL, Schiffman EL, Dworkin SF. The Research Diagnostic Criteria for Temporomandibular Disorders. IV: evaluation of psychometric properties of the Axis II measures. J Orofac Pain 2010;24:48-62.

Okeson JP (ed). Diagnostic classification of orofacial pain disorders. In: Orofacial Pain. Guidelines for assessment, diagnosis, and management. Quintessence, Carol Stream, 1996;45-52.

Okeson JP. Management of temporomandibular disorders and occlusion. St.Louise, MO; London: Mosby; 2008.

Ommerborn MA, Kollmann C, Handschel J, Depprich RA, Lang H, Raab WH-M. A survey on German dentists regarding the management of craniomandibular disorders. Clin Oral Invest 2010;14:137-144.

Pahkala RH, Laine-Alava MT. Do early signs of orofacial dysfunctions and occlusal variables predict development of TMD in adolescents? J Oral Rehabil 2002;29:737-743.

Palla S.Grundsätze zur Therapie des myoarthropathischen Schmerzes. Schmerz 2002;16:373-380.

Pettengill CA. A comparison of headache symptoms between two groups: a TMD group and a general dental practice group. Cranio 1999;1:65-69.

Plesh O, Stohler CS. Prosthetic rehabilitation in temporomandibular disorder and orofacial pain patients. Clinical problem solving. Dent Clin North Am 1992;36:581-589.

Pullinger AG, Seligman DA. Trauma history in diagnostic groups of temporomandibular disorders. Oral Surg Oral Med Oral Pathol 1991;71:529-534.

Pullinger AG, Seligman DA. Quantification and validation of predictive values of occlusal variables in temporomandibular disorders using a multifactorial analysis. J Prosthet Dent 2000;83:66-75.

Ramfjord SP, Ash MM. Reflections on the Michigan occlusal splint. J Oral Rehabil 1994;21:491-500.

Rammelsberg P, LeResche L, Dworkin SF, Mancl L. Longitudinal outcome of temporomandibular disorders: a 5-year epidemiologic study of muscle disorders defined by Research Diagnostic Criteria for Temporomandibular Disorders. J Orofac Pain 2003;17:9-20.

Raphael KG, Marbach JJ: Widespread pain and the effectiveness of oral splints in myofascial face pain. J Am Dent Assoc 2001;132:305-316.

Rasmussen BK, Jensen R, Schroll M, et.al. Epidemiology of headache in a general population–a prevalence study. J Clin Epidemiol 1991;11:1147-1157.

Rasmussen BK, Jensen R, Olesen J. Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 1992;46:443-446.

Reissman DR, John MT, Wassel RW, Hinz A. Psychosocial profiles of diagnostic subgroups of temporomandibular disorder patients. Eur J Oral Sci 2008;116:237-244.

Rider MS, Achterberg J, Lawlis GF, Goven A, Toledo R, Butler R. Effect of immune system imagery on secretory IgA. Biofeedback and Self-regulation 1990; 15: 317-333.

Rizzatti-Barbosa CM, Nogueira MT, de Andrade ED, Ambrosano GM, de Barbosa JR. Clinical evaluation of amitriptyline for the control of chronic pain caused by temporomandibular joint disorders. Cranio 2003;21:221-225.

Rollman GB, Gillespie JM. The role of psychosocial factors in temporomandibular disorders. Curr Rev Pain 2004;4:71-81.

Rothman KJ, Greenland S. Modern Eidemiology. Lippincott-Raven, Philadelphia, 1998.

Saliva Diagnostics. Version 2. Hamburg: IBL GmbH;2006.

Sarita PT, Kreulen CM, Witter D, Creugers NH. Signs and symptoms associated with TMD in adults with shortened detal arches. Int J Prosthodont 2003;16:265-270.

Schiffman EL, Fricton JR, Haley DP, Shapiro BL. The prevalence and treatment needs of subjects with temporomandibular disorders. J Am Dent Assoc 1990;120:295-303.

Schiffman EL, Ohrbach R, Truelove EL, Tai F, Anderson GC, Pan W, Gonzales YM, John MT, Sommers E, List T, Velly AM, Kang W, Look JO. The

Research Diagnostic Criteria for Temporomandibular Disorders: V: methods used to establish and validate revised Axis I diagnostic algorithms. J Orofac Pain 2010a;24:63-78.

Schiffman EL, Truelove EL, Ohrbach R, Anderson GC, John MT, List T, Look JO. The Research Diagnostic Criteria for Temporomandibular Disorders. I: overview and methodology for assessment of validity. J Orofac Pain 2010b;24:7-24.

Schindler J, Svensson P. Myofascial Temporomandibular Disorder Pain – Pathophysiology and Management. In: Türp JC, Sommer C, Hugger A (eds): The Puzzle of Orofacial Pain. Integrating Research into Clinical Management. Pain Headache. Basel, Karger, 2007;vol 15,pp 91-123.

Seedorf H, Seetzen F, Scholz A, Sadat-Khonsari MR, Kirsh I, Jüde HD. Impact of posterior occlusal support on the condylar position. J Oral Rehabil 2004;31:759-763.

Seligman DA, Pullinger AG. Analysis of occlusal variables, dental attrition and age for distinguishing healthy controls from female patients with intracapsular temporomandibular disorders. J Prosthet Dent 2000;83:76-82.

Seligman DA, Pullinger AG. Dental attrition models predicting temporomandibular joint disease or masticatory muscle pain versus asymptomatic controls. J Oral Rehabil 2006;33:789-799.

Severinsson Y, Bunketorp O, Wenneberg B. Jaw symptoms and signs and the connection to cranial cervical symptoms and post-traumatic stress during the first year after a whiplash trauma. Disabil Rehabil. 2010;32:1987-1998.

Seymor RA, Simpson JM, Charlton JE, Phillips ME. An evaluation of length and end-phrase of visual analogue scales in dental pain. Pain 1985;21:177-185.

Shankland WE. Migraine and tension-type headache reduction through pericranial muscular suppression: a preliminary report. Cranio 2001;19:269-278.

Shankland WE. Nociceptive trigeminal inhibition-tension suppression system: a method of preventing migraine and tension headaches. Compend Contin Educ Dent 2002;23:105-108.

Shifman A, Gross MD. Diagnostic targeting of temporomandibular disorders. J Oral Rehabil 2001;28:1056-1063.

Shokker RP, Hansson TL, Ansink BJJ. Craniomandibular disorders in patients with different types of headache. J Craniomandib Disord 1990a;4:47-51.

Shokker RP, Hansson TL, Ansink BJJ. The Result of Treatment of the Masticatory System of Chronic Headache Patients. Craniomandib Disord 1990b;4:126-130.

Shrout PE, Fleiss JL. Intraclass Correlations: Uses in Assessing Rater Reliability. Psychological Bulletin 1979;2:420-428.

Siegert R, Gundlach KKH. Stabilisationsschiene versus Entspannungsbehelf zur Behandlung myofazialer Schmerzen. Dtsch Zahnärztl Z 1989;44:17-19.

Sipilä K, Zitting P, Siira P, Laukkanen P, Järvelin MR, Oikarinen KS, Raustia AM. Temporomandibular disorders, occlusion, and neck pain in subjects with facial pain: a case-control study. Craniomanib Pract 2002;20:158-164.

Slade GD, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim RB, Belfer I, Max MB, Goldman D, Maixner W. Influence of psychological factors on risk of temporomandibular disorders. J Dent Res 2007;86:1120-1125.

Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. J Pain 2003;4:109-121.

Sommer C. Pharmakologische Behandlung orofazialer Schmerzen. Schmerz 2002;16:381-388.

Stapelman H, Turp JC. The NTI-tss device for the therapy of bruxism, temporomandibulaar disorders, and headache – Where do we stand? A qualitative systematic review of the literature. BMC Oral Health 2008;8:22.

Stegenga B, de Bont LG. TMJ disc derangements. In: Temporomandibular disorders: an evidence-based approach to diagnosis and treatment. Laskin DM, Greene cs, Hylander WL (eds). 2006, Chicago, Quintessence Pub,125-136.

Suvinen TI, Reade PC, Kemppainen P, Könönen M, Dworkin SF. Review of etiological concepts of temporomandibular pain disorders: towards a biopsychosocial model for integration of physical disorder factors with psychological and psychosocial illness impact factors. Eur J Pain 2005;9:613-633.

Svensson P. Muscle pain in the head: overlap between temporomandibular disorders and tension-type headache. Curr Opin Neurol 2007;20:320-325.

Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pain-pressure thresholds and stimulus-response curves. J Orofac Pain 1995;9:347-356.

Svensson P, Caims BE, Wang K, Arendt-Nielsen L. Injection of nerve growth factor into human masseter

muscle evokes long-lasting mechanical allodynia and hyperalgesia. Pain 2003;104:241-247.

Svensson P, Jadidi F, Arima T, Baad-Hansen L, Sessle BJ. Relationship between craniofacial pain and bruxism. J Oral Rehabil 2008;35:524-547.

Truelove E, Hanson-Huggins K, Mancl L, Dworkin SF. The efficacy of traditional, low-cost and non-splint therapies for temporomandibular disorder. Jam Dent Assoc 2006;137:1009-1107.

Truelove E, Pan W, Look JO, Mancl LA, Ohrbach RK, Velly AM, Huggins KH, Lenton P, Shiffman EL. The Research Diagnostic Criteria for Temporomandibular Disorders. III: validity of Axis I diagnoses. J Orofac Pain 2010;24:35-47.

Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337-345.

Turner JA, Dworkin SF, Mancl L, Huggins KH, Truelove EL. The roles of beliefs, catastrophizing, and coping in the functioning of patients with temporomandibular disorders. Pain 2001;92:41-51.

Turner JA, Mancl L, Aaron LA. Short- and long-term efficacy of brief cognitive-behavioral therapy for patients with chronic temporomandibular disorder pain: A randomized, controlled trial. Pain 2006;121:181-194.

Turner JA, Whitney C, Dworkin SF, Massoth D, Wilson L. Do changes in patient beliefs and coping strategies predict temporomandibular disorder treatment outcomes? Clin J Pain 1995;11:177-188.

Türp JC, Komine F, Hugger A. Efficacy of stabilization splints for the management of patients with masticatory muscle pain: a qualitative systematic review. Clin Oral Invest 2004;8:179-195.

Türp JC, Strub JR. Prosthetic rehabilitation in patients with temporomandibular disorders. J Prosthet Dent 1996;76:418-423.

Valdimarsdottir HB, Stone AA. Psychosocial factors and secretory immunoglobulin A (review). Crit Rev Oral Biol Med 1997;8:461-474.

Vallon D, Ekberg EC, Nilner M, Kopp S. Short term effect of occlusal adjustment on craniomandibular disorders including headaches. Acta Odontol Scand 1991;49:89-98.

Vallon D, Ekberg EC, Nilner M, Kopp S. Occlusal adjustment in patients with craniomandibular disorders including headache. A 3- and 6-month follow-up. Acta Odontol Scand 1995;53:55-59.

Vallon D, Nilner M, Soderfeldt B. Treatment outcome in patients with craniomandibular disorders of muscular origin: A 7-year follow-up. J Orofac Pain 1998;12:210-218.

Van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev 2000;2:CD000396.

Velly AM, Gornitsky M, Philippe P. Contributing factors to chronic myofascial pain: a case-control study. Pain 2003;104:491-499.

Vining RF, McGinley RA. The measurement of hormones in saliva: possibilities and pitfalls. J Steroid Biochem 1987;27:81-94.

Visscher CM, Lobbezoo F, Naeije M. Comparison of algometry and palpation in the recognition of temporomandibular disorder pain complaints. J Orofac Pain 2004;18:214-219.

Visscher CM, Naeije M, De Laat A, Michelotti A, Nilner M, Craane B, Ekberg E, Farella M, Lobbezoo F. Diagnostic accuracy of temporomandibular disorder pain tests: a multicenter study. J Orofac Pain 2009;23:108-114.

Von Korff M, Dworkin SF, LeResche L, Kruger A. An epidemiologic comparison of pain complaints. Pain 1988a;32:173-183.

Von Korff M, Dworkin SF, LeResche L, Kruger A. Epidemiology of temporomandibular disorders: TMD pain compared to other common pain sites. In: Dubner R, Gebhart GF, Bond MR (eds): Pain Research and Clinical Management. Amsterdam, Elsevier, 1988b, pp 506-511.

Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133-149.

Wahlund K, List T, Larsson B. Treatment of temporomandibular disorders among adolescents: A comparison between occlusal appliances, relaxation training and brief information. Acta Odontol Scand 2003;61:203-211.

Wang MQ, Xue F, He JJ, Chen JH, Chen CS, Raustia A. Missing Posterior Teeth and Risk of Temporomandibular Disorders. J Dent Res 2009;88:942-945.

White BA, Williams LA, Leben JR. Health care utilization and cost among health maintenance organization members with temporomandibular disorders. J Orofac Pain 2001;15:158-169.

Wright E, Anderson G, Schulte J. A randomized clinical trial of intraoral soft splints and palliative treatment for masticatory muscle pain. J Orofac Pain 1995;9:192-199.

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Wänman A. Longitudinal course of symptoms of craniomandibular disorders in men and women. A 10-year follow-up study of an epidemiologic sample. Acta Odontol Scand 1996;54:337-342.

Wänman A, Agerberg G. Headache and dysfunction of the masticatory system in adolescents. Cephalalgia 1986;6:247-255.

Wänman A, Agerberg G. Etiology of craniomandibular disorders: evaluation of some occlusal and psychosocial factors in 19-year-olds. J Craniomandib Disord 1991;5:35-44.

Yap AU, Tan KB, Chua EK, Tan HH. Depression and somatization in patients with temporomandibular disorders. J Prosthet Dent 2002;88:479-484.

Ylinen J, Häkkinen A, Nykänen M, Kautiainen H, Takala EP. Neck muscle training in the treatment of chronic neck pain: a three-year follow-up study. Eura Medicophys 2007;43:161-169.

Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val^{158}met genotype affects μ-opioid neurotransmitters responses to a pain stressor. Science 2003;299:1240-1243.

Österberg T, Carlsson GE, Wedel A, Johansson U. A cross-sectional and longitudinal study of craniomandibular dysfunction in an elderly population. J Craniomandib Disord 1992;6(4):237-245.