Salivary cortisol and psychological factors in women with chronic and acute orofacial pain

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Summary

Aim: To investigate psychological factors and cortisol secretion in women with chronic and acute orofacial pain (OP) as well as in a healthy and pain-free control group.

Methods: A total of 79 female patients were included in the study, 28 with chronic OP (a diagnosis of myofascial pain according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), 24 with acute OP (mainly toothache) and 27 pain-free controls. The current pain intensity was assessed on a 0-10 numeric rating scale. The participants were evaluated by the Symptom Checklist-Revised 90R included in the RDC/TMD axis II questionnaire for levels of depression and unspecific physical symptoms, the Perceived Stress Scale and some general questions. Morning saliva was collected from all participants for analyses of cortisol levels.

Results: Patients with chronic OP reported significantly higher levels of depression, non-specific physical symptoms and perceived stress compared to patients with acute OP (Ps < 0.001), in spite of similar pain levels (median = 5 in both groups). There were no significant differences between the patients with acute OP and controls. The cortisol levels among the three patient groups were similar with no significant group differences.

Conclusion: The present study showed that patients with chronic OP had higher levels of depression, non-specific physical symptoms and perceived stress compared to the patients with acute OP and pain-free individuals, but this did not influence the adrenocortical activity measured as saliva cortisol level. Patient with acute OP did not differ to the controls in psychological factors.

Keywords: Pain, temporomandibular disorders, salivary cortisol, behavioral symptoms, perceived stress scale.
Sammanfattning [Summary in Swedish]

**Syfte:** Att studera de psykologiska förhållandena samt nivån av stresshormonet kortisol hos kvinnor med kronisk och akut ansiktssmärta och jämföra dessa med en smärtfri kontrollgrupp.

**Metod:** Totalt deltog 79 kvinnliga patienter i studien. 28 patienter med kronisk ansiktssmärta (samtliga uppfyllde diagnosen för myofaciell smärta enligt gällande diagnostiska kriterierna för temporomandibulär dysfunktion (RDC/TMD), 24 patienter med akut ansiktssmärta (i huvudsak tandvårk) och 27 kontroller ingick i studien. Deltagarnas smärtintensitet uppmättes med en 10 gradig numerisk skala. Graden av depression och somatisering bedömdes med hjälp av Symptom Checklist 90R som utgör en del av RDC/TMD axel II. Stressnivån bedömdes med hjälp av Percived Stress Scale. Salivprov togs från alla deltagare för analys av kortisolnivån.

**Resultat:** Trots att patienter med akut och kronisk ansiktssmärta uppgav likartad smärtintensitet (median=5 i både grupperna) så rapporterade patienter med kronisk ansiktssmärta signifikant högre nivåer av depression, somatisering och självupplevd stress i jämförelse med patienter med akut käksmärta (Ps <0.001. De tre patientgrupperna som ingick i studien uppvissade jämförliga kortisolnivåer, således kunde inga signifikanta skillnader identifieras mellan grupperna.

**Slutsats:** Studien visar att patienter med kronisk ansiktssmärta upptäcker högre nivåer av depression, somatisering och psykologisk stress i jämförelse med patienter med akut käksmärta och friska kontroller. Studien visar vidare på att kortisolutsöndringen hos de tre grupperna är jämbördig.

Slutligen visar studien på att patienter med akut käksmärta inte skiljer sig från de friska kontrollerna avseende de psykologiska variablerna.

**Nyckelord:** smärta, temporomandibular dysfunktion, saliv kortisol, psykologiska sytoment, skala för självupplevd stress.
Pain in the orofacial region is the most common reason for dental care seeking amongst the adult population. The pain can either be acute or chronic. Acute pain has a warning and protective function for the body and is the symptom of an underlying pathological process. Symptom-oriented therapy generally results in pain relief. On the other hand, persistent or chronic pain has lost this warning and protective function and is defined as an independent illness. (1) Chronic orofacial pain (OP) affects up to 10-15% of the adult population and is most commonly due to temporomandibular disorders (TMD). (2-3)

TMD shares the major characteristics of other common chronic pain conditions, notably headaches and back pain. It is widely recognized that psychological factors may be involved in the pain perception process. Although the underlying etiology and pathogenesis of TMD have not been completely established, they are considered to be multifactorial involving psychological, psychosocial and behavioral factors.(4-5) The role of psychosocial factors in different stages of TMD has been intensively investigated over the past decade and many studies suggest that depression, non-specific physical symptoms (somatization) and stress play a role in the predisposition, initiation and perpetuation of TMD and also in the response of TMD patients to treatment. (5-12) Studies have shown that there is a high degree of comorbidity between TMD and depression. Depending on whether samples are taken from the community or orofacial specialist clinics and also which type of diagnostic criteria that has been used, depression was found in 25-60 % of the patients suffering from TMD. (4,5,10,13-14) The proportion of depression is also significantly higher in subjects with symptoms of TMD compared with asymptomatic subjects.(13) Among the TMD symptoms, those related to pain has the most significant relations to the depression rate. (11,15)

Further, there is also evidence that altered basal and stress-induced hypothalamic-pituitary-adrenal (HPA) activity may exist in chronic painful conditions. (8,16,17) In addition, high perceived stress level is reported to correlate with high cortisol level.(18,19) However, research that actually has evaluated the influence of the HPA axis in chronic OP patients is relatively scarce and show contradictory results. Some findings suggest that patients with a TMD diagnosis exhibit altered HPA dynamics compared to healthy controls, (20-23) while others report no significant differences when compared to controls. (20,24,25) In fact, one study reported that there might be two subgroups of TMD patients, one that respond with increased
cortisol release in response to stress and another that show a dysfunctional cortisol response. (22)

The prevalence and role of psychological factors might vary depending on the pain status of the patient, and the longer the pain persists the more opportunity there is for psychological factors to be involved either in the pain itself or in the disability caused by the pain. (13) Most studies regarding psychological factors in chronic OP compares exclusively patients with healthy controls. To our knowledge no studies have systematically examined if patients with chronic OP differ from patients with acute OP regarding basal HPA activity, perceived stress and psychosocial factors. Since pain act as a potential stressor and affects physical as well as psychological systems it would be of interest to compare these two patient groups. We hypothesized 1) that patients with OP, either if it is acute or chronic, have increased levels of perceived stress with associated elevated cortisol levels compared to pain-free controls, and 2) that the levels of depression and unspecific physical symptoms are higher in patients with chronic OP compared to patients with acute OP.

Aim
The aim of the present study was to investigate the saliva cortisol level and psychological factors in women with chronic and acute OP as well as in a pain-free control group.
Materials and Methods

Subjects
Subjects included in the study were patients with chronic OP (n= 28), acute OP (n= 24) and pain-free individuals (n= 27). The age range of the patients was 20 to 80 years, with most patients in the 40 to 60 years age group. Attempts were made to match participants in the groups according to age. A sample size calculation showed that 25 patients in each group would be sufficient to detect groups’ differences in the magnitude of 1 SD with a power of almost 90% at a significance level of 5%.

The patients with chronic OP were recruited from patients referred to the Orofacial pain clinics at the Department of Dental Medicine at Karolinska Institutet, Huddinge and the Eastman Institute, Stockholm, Sweden. Inclusion criteria were a diagnosis of myofascial pain according to the RDC/TMD criteria (axis I) (26) and a pain duration of at least three months.

The patients with acute OP and the control group were recruited from patients seeking treatment at the undergraduate dental clinic, department of Dental Medicine, Karolinska Institutet, Huddinge, Sweden. Following the guidelines of the International Association for the Study of Pain (IASP) acute pain was defined as a short lasting pain which consider a symptom of disease or injury. (27) Inclusion criterion for the patients with acute OP was accordingly pain of less than 10 days duration for which the subjects sought acute dental care.

Patients seeking dental care for other reasons than pain, e.g. fracture of filling, regular dental examination, prosthetics rehabilitation and with a total absence of orofacial pain served as control group. Participants in the control group where screened for pain in the orofacial region to ensure that they had not received treatment for acute dental pain or TMD pain during the previous month.

Exclusion criteria for all study participants were generalized pain, systemic inflammatory disease, neuropathic pain, presence of blood in the saliva sample, local or systemic treatment with glucocorticoids, major systemic illnesses and not speaking or understanding the Swedish language. In an effort to reduce differences in cortisol secretion, degree of stress, stress coping strategies and psychological variables, all subjects in the study were female.
The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2011/1955-31/2) and followed the guidelines according to the Declaration of Helsinki. The subjects received clarifications regarding the objectives and procedures of the study and signed terms of informed consent, agreeing to their participation.

**Questionnaire**

The participants were evaluated by the Swedish version of the Research Diagnostic Criteria for TMD (RDC/TMD) axis II questionnaire, (26) the Perceived Stress Scale (PSS-14), demographic variables, and some general questions related to the measurement of salivary cortisol. Frequency of analgesics taken the previous month (0 = never, 1 = 1-2 times/month, 2 = once/week, 3 = several times/week and 4 = daily) was also assessed. Subjects were further asked if they had smoked, consumed any food or drink or performed any oral care during the last hour. Finally, they were asked if they used oral contraceptives or other hormone replacement therapy, since studies have shown that the total plasma cortisol levels are increased in estrogen-treated women. (28-31)

**PAIN INTENSITY**

Pain intensity was assessed using the first question from the Graded Chronic Pain Scale included in the RDC/TMD questionnaire. This question assesses the current pain level on a 0-10 numerical rating scale, where 0 = no pain and 10 = worst imaginable pain.

**PSYCHOLOGICAL SYMPTOMS**

The Symptom Checklist 90-revised (SCL-90R), included in the RDC/TMD questionnaire was used for assessment of depression and somatization among subjects. The scale consists of 32 items, 20 items measuring depression and 12 items for measuring somatization. Each item in the SCL-90R gives a numerical value between 0 and 4. These values are then summarized and divided with the number of items in each sub-group and results in maximum subscale scores of 4.0, with higher scores indicating higher levels of distress. The axis II psychological profile measures do not provide definitive clinical psychiatric diagnoses, however they are reliable and valid indicators of depression and somatization. (32) The RDC/TMD has been used extensively in international clinical research environments in the standardized evaluation of TMD. The normal reference value for depression according to the SCL-90R is below 0.535 and for somatization
with pain < 0.5. The normal reference value for somatisation without pain is < 0.428.

PERCEIVED STRESS

The PSS is a psychological instrument for measuring the perception of stress. It was designed by Cohen et al. to measure the degree of which individuals appraise situations in their lives as stressful. (33) The 14-item instrument is intended to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct questions about current levels of experienced stress. Furthermore, the questions are quite general in nature and consequently relatively free of content specific to any sub population group. The PSS questionnaire addresses issues such as feelings and thoughts during the last month. In each case, participants are asked how often they have felt in a certain way. Subjects rate the items on a five-grade Likert scale (0-4) with higher scores reflecting greater level of perceived stress. The PSS final score is obtained by reversing the scores on the seven positive items, and then summing across all 14 items. Cohen et al. suggest PSS to examine the role of non-specific appraised stress in the etiology of disease and behavioral disorders, and as an outcome measure of mental stress. (33) The Swedish version of the PSS, which was used in this study, has been found to be a reliable and valid instrument.34 Normal levels in PSS score have been calculated to 23.67 in healthy subjects. (33).

Cortisol assessment and biochemical analysis

It has been shown in many studies that salivary cortisol is a valid indicator for cortisol concentration in blood serum and that psychological stress also affects the salivary cortisol level. (22,35-38) The salivary cortisol levels are unaffected by salivary flow rate, composition of the saliva concerning serous/mucous content and the present of salivary enzymes. (39,40) All participants in the study had refrained from smoking, eating and drinking a minimum of 30 minutes prior to the saliva sampling.

Saliva was collected in polypropylene tubes during a period of 3-9 minutes depending on the patient's individually saliva flow rate. Participants were instructed to spit whole salvia through a short polypropylene funnel into the tube, while being in a normal sitting position. In order to minimize the effect of the diurnal variation in the cortisol secretion all samples were collected between 07.45 and 12.15 am. The samples were immediately refrigerated
and frozen within five hours (-20° C). It was assured that the storing time did not exceed 2 years. Since cortisol is relatively stable in saliva, this procedure has been reported to be unproblematic. (41,42)

Before analyses, the saliva samples were thawed and centrifuged at 1500 x g (@3000 rpm) for 15 minutes. All samples were assayed in duplicate using the Salivary Cortisol Enzyme Immunoassay Kit according to the instructions of the manufacturer (Salimetrics, State College, PA, USA). Cortisol data presented in this study are the average value of the duplicate cortisol analyses. Sensitivity of the assay was < 0.003 μg/dL.

**Statistical analyses**

Differences between groups in frequency distribution were tested with Chi-square test. One-way analysis of variance (ANOVA) on ranks (Kruskall-Wallis test) was used to analyze for differences in variables between groups since most variables did not show a normal distribution or were assessed on an ordinal scale. The Dunn’s methods for multiple comparisons were used as post-hoc test when the ANOVA indicated significant differences. To analyze subgroups within the chronic OP group a median split was performed. 20 Differences between these two subgroups, i.e., patients with high cortisol levels (HC) and low cortisol level (LC) were analyzed with the Mann-Whitney U-test and Chi-square test. Correlations between variables were tested for statistical significance with Spearman Rank Correlation test, adjusted for multiple comparisons according to Bonferroni. Descriptive data are presented as mean and standard deviation (SD) or median and interquartile range (IQR). For all analyses, the significance level was set at P < 0.05. The statistical analyses were performed using SigmaStat v. 11.0 (Systat software Inc, Chicago, IL, USA).
Results

Subjects
Out of the 94 patients that were asked to participate in the study, 15 patients refrained because of the effort and time involved, therefore data was collected from 79 patients, 28 patients with chronic OP, 24 patients with acute OP and 27 healthy controls. Despite attempts to match the groups according to age, the mean age of the chronic OP group was slightly lower than that of the acute OP group and controls. However, no statistically significant differences were found between the three patient groups regarding age, number of smokers, number of oral contraceptive/hormone replacement therapy users, education level and marital status. Further no significant differences were found between the times of saliva sampling between groups. A significantly larger proportion of patients with gainful employments were found in the acute OP group compared to the other groups (P < 0.001). Descriptive characteristics of the subjects are presented in Table 1.

Pain duration, pain intensity and analgesics consumption
The pain duration among patients with chronic OP was in average 5.3 years (SD 7.9), while the corresponding duration was 5 days (SD 2.6) among patients with acute OP. The current pain intensity differed significantly between groups, with both groups of pain patients having higher levels than controls (Table 2). None of the controls reported any current OP. There were no significant differences between the chronic and acute OP group in pain intensity. There were significant differences in analgesic consumption between groups (P < 0.001). The post-hoc test showed that patients with chronic and acute OP reported more frequent use of analgesic during the previous month compared to controls (P < 0.05). Most patients used non-prescribed pain relievers e.g. paracetamol and NSAIDs (ibuprofen, acetylsalicylic acid, diclofenac), and only one patient each in the chronic and acute OP groups used combinations of paracetamol/NSAID and codeine.
Table 1. Demographic characteristics of female patients in patients with chronic and acute orofacial pain (OP) as well as in a control group of healthy women. The figures show the number (%) of patients unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>Chronic OP n=28</th>
<th>Acute OP n=24</th>
<th>Controls n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean, SD)</td>
<td>42.3 (SD 15.8)</td>
<td>46.7 (SD 13.8)</td>
<td>45.7 (SD 20.2)</td>
</tr>
<tr>
<td>Average sampling time</td>
<td>10.05 am</td>
<td>10.10 am</td>
<td>10.16 am</td>
</tr>
<tr>
<td>Smoker</td>
<td>1 (4)</td>
<td>4 (15)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Oral contraceptives usage</td>
<td>5 (22)</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>2 (7)</td>
<td>5 (21)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>High school education</td>
<td>16 (57)</td>
<td>13 (54)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>University degree</td>
<td>9 (32)</td>
<td>5 (21)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gainful employment</td>
<td>8 (29)</td>
<td>18 (75)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Student</td>
<td>7 (25)</td>
<td>1 (4)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Housewife</td>
<td>3 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Early pension</td>
<td>3 (11)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Sick leave</td>
<td>3 (11)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Retirement pension</td>
<td>4 (14)</td>
<td>3 (12)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/partner</td>
<td>19 (68)</td>
<td>13 (54)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Single</td>
<td>5 (18)</td>
<td>8 (33)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Divorced</td>
<td>2 (7)</td>
<td>3 (12)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Widow</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Table 2. Current pain intensity according to NRS (0-10) and frequency of analgesic-use in female patients with chronic and acute orofacial pain (OP) as well as in a control group of healthy women. The figures show the number (%) of patients unless other is stated.

<table>
<thead>
<tr>
<th></th>
<th>Chronic OP n=28</th>
<th>Acute OP n=24</th>
<th>Controls n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5 (4)</td>
<td>5 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>consumption (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1 (4)</td>
<td>3 (13)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>1-2 times/month</td>
<td>6 (21)</td>
<td>5 (21)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>1 time/week</td>
<td>3 (11)</td>
<td>4 (17)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>&gt;1 times/week</td>
<td>6 (21)</td>
<td>8 (33)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Daily</td>
<td>8 (29)</td>
<td>4 (17)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Psychological variables

The PSS scores are illustrated in Fig. 1A. As can be seen, patients with chronic OP showed increased PSS score compared to the normal range (median 28.0; IQR 13). The groups differed significantly in PSS score (P = 0.027). Patients with chronic OP reported higher levels of perceived stress compared with patients having acute OP and controls (P < 0.05). There were no differences between patients with acute OP and controls in PSS score. The psychological characteristics of the subjects are illustrated in Fig. 1B-D. There was a statistically significant group difference for depression (P < 0.001) and somatization both with and without pain (Ps < 0.001). The post-hoc tests showed that patients with chronic OP had significantly higher levels of somatization and depression compared with acute OP and controls (P < 0.05). No differences were found between patients with acute OP and controls.
Figure 1. Box plots showing (A) the stress level according to the perceived stress scale (PSS) as well as levels of depression (B), non-physical symptoms (somatization) with (C) and without (D) pain according to the symptom checklist-90 revised (SCL-90R) in 28 female patients with chronic orofacial pain (COP), 24 with acute orofacial (AOP) and in 27 healthy women (CTR). The boundary of the box indicates the 25th and 75th percentiles, the line within the box marks the median and the whiskers indicate the 90th and 10th percentiles. *Significant differences (Dunn's test, P < 0.05).

Salivary cortisol

The median (IQR) cortisol level did not differ significantly between groups and was 0.210 (0.288) µg/dl in the chronic OP patients, 0.250 (0.239) µg/dl in the acute OP patients and 0.211 (0.149) µg/dl in the controls. The cortisol values showed great individual variations within groups. The patients who had their saliva samples taken before 10.00 am (n = 30) showed greater variations (0.13 – 1.359 µg/dl) in salivary cortisol than the patients who had their samples taken at 10.00 am and afterwards (n = 49) (0.073-0.869 µg/dl). Their median (IQR) cortisol level was also higher, 0.36 (0.28) µg/dl
compared to 0.20 (0.15) µg/dl (P < 0.001). There was no difference between
groups in the saliva sampling time. Only six patients showed values below
0.094 µg/dl (morning reference values for women in ages 31-50 years are
0.094-1.515 µg/dl), while the rest were within published references levels.
(35) These six patients all had their saliva samples taken after 10.00 am.
Since a previous study reported two subgroups of TMD patients,22 we also
tested if there were any differences in cortisol level within chronic OP
patients by dividing the group by a median split. The median (IQR) cortisol
level in the HC group was 0.421 (0.189) µg/dl and in the LC group 0.134
(0.046) µg/dl). There were no significant differences in mean age, saliva
sampling time, number of patients using hormone replacement therapy,
depression and somatisation level, or PSS score between these two sub-
groups (Table 3).

Table 3. Descriptive variables, psychological symptoms and salivary cortisol level (µg/dl) in
28 female patients with chronic orofacial pain divided into a high cortisol (HC) and a low
cortisol (LC) group by a median split. The values shown are median (interquartile range)
unless other is stated.

<table>
<thead>
<tr>
<th></th>
<th>HC n=14</th>
<th>LC n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean, SD)</td>
<td>40.2 (SD 13)</td>
<td>44.2 (SD 17.3)</td>
</tr>
<tr>
<td>Average sampling time</td>
<td>9.55 am</td>
<td>10.48 am</td>
</tr>
<tr>
<td>Oral contraceptives usage (n)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pain level, NRS</td>
<td>5 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Psychological variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.1 (1.81)</td>
<td>1.2 (0.97)</td>
</tr>
<tr>
<td>Somatization with pain</td>
<td>1.8 (1.85)</td>
<td>1.4 (0.98)</td>
</tr>
<tr>
<td>Perceived stress</td>
<td>27.5 (14.5)</td>
<td>28.5 (13.5)</td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td>0.412 (0.189)</td>
<td>0.134 (0.046)*</td>
</tr>
</tbody>
</table>

NRS= numeric rating scale (0-10). *P < 0.001
Correlations

Correlation analyses showed that the levels of depression and somatization with and without pain were positively correlated (rs = 0.833 and rs = 0.841, n = 77, P < 0.001, respectively). The levels of depression and somatisation with and without pain were further positively correlated to the PSS score (rs = 0.738, rs = 0.605, and rs = 0.604, respectively, n = 77, P < 0.001 for all), but there were no significant correlations between saliva cortisol levels on one hand and PSS score, depression, or somatisation levels on the other hand.
Discussion

The objectives of the present study were to investigate whether there were any differences in adrenocortical activity, depression, somatization and perceived stress levels between patients with chronic OP, acute OP and healthy pain-free controls. To our knowledge, this is the first study examining the relationship between adrenocortical activity and psychological variables in patients with acute OP. We had hypothesized that pain functions as a stress factor and thus, that patients with chronic OP and acute OP would show higher levels of perceived stress and salivary cortisol than pain-free controls. However, while we found higher levels of depression, somatization and perceived stress in the patients with chronic OP compared to patients with acute OP and controls, the latter did not differ from controls in PSS score and there were no differences between any groups in cortisol levels. Thus our hypotheses were partly rejected.

Patient sample

Although the controls and patients with acute OP were slightly older than patients with chronic OP, there were no significant differences between groups. As illustrated in Table 1 the three patient groups were also relatively homogeneous in their use of hormone replacement therapy, education levels, and marital status, without significant differences between them. However, although more patients with acute OP had gainful employment than in the other groups, we consider the groups comparable with respect to these background factors.

Both pain groups reported current pain of moderate and similar intensity. It must be emphasized though, that the pain levels might have been reduced because of analgesics use in the patients with chronic and acute OP.

Psychological factors

It is known that elevated levels of psychological stress have the potential to intensify perceived pain, reduce an individual’s capacity to tolerate pain and affect overall wellbeing. (8,16) In the present study we found that the chronic OP patients had markedly higher levels of perceived stress compared to the other groups. The perceived stress level among the acute OP patients, however, did not differ from controls and was in agreement with the levels reported by Cohen et al. (33) in the general population. This was unexpected, since we had hypothesized that being in pain per se should be stressful. However, patients with acute OP may respond differently to the questionnaire, since they expect the pain to be relieved after treatment. In
addition, correlation analysis revealed that the PSS score was positively related to the depression and somatization levels. This result shows that these instruments are interconnected.

In addition to stress it is accepted that other psychological factors, such as depression and somatization play a role in the etiology and maintenance of chronic pain, and are essential elements to consider in the treatment and further care of these patients. (23,20) Dworkin et al., showed that depression was more common in chronic pain patients than in healthy controls, and proposed the idea that depression may be rather a consequence of the presence of chronic pain (43) and accordingly not a predisposing factor as some authors have suggested. Other studies that assessed psychological distress in females with TMD also found a close association between pain and psychosocial impairment. (14,44) The high levels of depression and somatization in patients with chronic OP in our study are in agreement with those findings. Of the TMD diagnoses, myofascial pain has been most associated with high depression levels, which explain the high depression level found in this study. (45)

However, none of the previous studies included patients with acute OP. We found that patients with acute OP showed levels of depression and somatization that were almost in the normal range, and did not differ from those of the controls, in spite of pain levels similar to the patients with chronic OP. Although it has been observed that patients suffering from depression are more likely to report higher pain levels than those without depression, even if there is no obvious medical base for the difference in pain intensity, (46) this was as expected. A possible explanation, which also has been discussed in patients with more prolonged pain, could be that the duration of the pain experience has a direct effect on the psychological variables; the longer the pain persists the more opportunity there is for the psychological factors to be involved either in the pain itself or in the disability caused by the pain. (13)

Yap et al used the RDC/TMD to assess psychological factors in subgroups of TMD patients. The results revealed that patients diagnosed with myofascial pain and arthralgic joint related conditions had significantly higher levels of somatization than patients diagnosed with only disc displacement, suggesting that the pain experienced by a number of TMD patients may be somatic expressions of psychiatric and psychosocial disturbance. (10) In our study we found a strong positive correlation between somatization with and without pain and depression. The significant and strong correlation between depression and somatization without pain
items, suggest that pain experienced by some chronic OP patients may be a somatic expression of psychological disturbance. However, there was a large inter-individual variation in depression level, especially in the chronic OP group.

**Adrenocortical activity**

Psychological stress is also known to induce various adaptive responses of physiologic systems, including an increased activity in the HPA system, which promotes cortisol secretion from the adrenal cortex. Increased activation of the HPA axis is a normal response to stress and has widespread effects that adjust homeostasis, and therefore, improve the ability of the organism to survive under conditions of stress. Many studies have been conducted to evaluate the HPA activity in patients with chronic painful condition. Some findings do suggest that patients with TMD exhibit altered HPA dynamics in relation to healthy controls. For instance, TMD patients exhibited increased cortisol level in response to experimental stress and tend also to demonstrate 30 to 50% higher daytime plasma-cortisol levels when compared to controls. In contrast, other studies have shown no significant differences in the cortisol profile between TMD patients and controls.

In the present study the median salivary cortisol level among subjects was similar in the three patient groups, accordingly no significant differences in basal cortisol level could be found between groups. Patients with acute OP had marginally higher levels of salivary cortisol, which most likely could indicate a central activation of the HPA axis and could represent a physiologic response to the acute stressor in the form of acute pain. It is known that activation of the HPA axis in acute stress is associated with analgesia, and that the corticotropin-releasing hormone can affect pain processes both centrally and peripherally. Chronic OP may also act as an activator of the HPA axis, although pain intensity was not correlated with the cortisol levels in the current study. Neither was there any association between psychological variables and cortisol levels, which also is in line with some earlier findings. The fact that there were no differences in the cortisol secretion between chronic OP patients who reported higher levels in psychological variables, e.g. depression, somatization and stress, and controls does not exclude the possibility of a dysregulation in the HPA axis among patients with chronic OP. The cortisol secretion follows a diurnal variation which is complex and furthermore the secretion is affected by multiple factors. A more comprehensive evaluation of the cortisol
secretory activity over the circadian cycle is perhaps necessary to reveal any significant differences between groups.

Jones et al. found that some TMD patients’ hyper-secreted cortisol when they were exposed to experimental stress, while others had a deficient cortisol secretion compared to healthy controls. However, their cortisol levels did not differ at baseline. A subgroup analysis of the chronic OP group in this study showed that HC patients did not differ from the patients with LC with respect to age, saliva sampling time, use of hormone-replacement therapy, pain level or psychological variables. In our study all the participants were examined when visiting the dental office and were accordingly exposed to a somewhat stressful situation. Even though the HC patients had twice as high levels of depression, somatization and perceived stress compared to the LC patients, there were no significant differences between the subgroups. On the other hand, the study was not powered for subgroups analyses, why it cannot be excluded that significant differences would occur with a larger patient sample. Further, since very few patients used hormone replacement therapy this factor should not have affected the results. This suggests that the linkage between biological and psychological factors may vary within the chronic OP patients. Further investigations of the association between psychological factors, cortisol response and pain are needed to elucidate the role and effects of the HPA axis in patients suffering from chronic OP.

**Study limitations**

Some limitations have to be considered when discussing the results of the present study. The subjects with chronic OP were recruited at specialist clinics and may differ from patients’ in general clinical practice, from where the acute OP and controls were recruited. Additionally, patients were not screened for the use of antidepressant drugs, but it was assured from the anamnesis that they did not suffer from any major illnesses apart from their orofacial pain. However, we cannot exclude that some patients might have used antidepressant drugs and that they did not disclose it to the dentist. We strived to age match the groups according to age, but were not fully successful in this. The chronic OP patients were slightly younger than the acute OP patients due to the generally younger patients with TMD related problems compared to patients with acute OP. This could also have affected our results. Nevertheless, there were no significant differences in age between the groups so we consider this age difference to be without major importance.
Weakness with the salivary measurement could be that we did not control for menstrual phase; however according to some authors there is no association between the phase of the menstrual cycle and the cortisol level. Furthermore for a reliable measurement it had been preferable to take the saliva samples at the exactly same time, but this was not possible of practical and ethical reasons due to the inclusion of patients with acute OP. Thus, this limitation is acceptable. It may also be discussed if significant differences between groups in saliva cortisol levels could be obtained with a larger patient sample. A post-hoc analysis based on the results from the study show that 138 patients would be needed to detect a significant difference between groups at the 5% level with a power of 0.8.

**Conclusions**

The results from the present study show that patients with chronic OP have higher levels of depression, somatization and perceived stress compared to patients with acute OP and pain-free individuals and that these factors correlate positively to each other. However, these higher levels were not associated with increased adrenocortical activity, since there were no significant differences in the cortisol level between groups. No significant differences were found between patients with acute OP and controls, supporting the assumption that pain of short duration does not alter the psychological profile.
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