Pain and Pain-Related Interference Associated with Recurrent Aphthous Ulcers

Jeffrey J. Sherman, PhD
Assistant Professor
Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington

Roland Barach, PhD
Psychologist
Mercer Island, Washington

Kellie K. Whitcomb, CDA
Study Coordinator
Regional Clinical Dental Research Center
University of Washington School of Dentistry
Seattle, Washington

Jeffrey Haley, BA, BS, JD
President
ORAHEALTH
Bellevue, Washington

Michael D. Martin, DMD, PhD
Associate Professor
Department of Oral Medicine
University of Washington School of Dentistry
Seattle, Washington

Correspondence to:
Dr Jeffrey J. Sherman
Department of Oral Medicine
University of Washington School of Dentistry
Box 356370
Seattle, WA 98195
E-mail: jeffreys@uwashington.edu

Aims: *(1) To use psychometrically sound measures to characterize the pain levels and pain-related interference associated with recurrent aphthous ulcers (RAU); (2) to determine whether subjects with RAU report clinically significant psychologic symptoms; and (3) to examine the relationships between physical characteristics and self-reported psychologic symptoms, pain, and pain-related interference.* ***Methods:*** *Forty-seven subjects with RAU and an active ulcer completed the Graded Chronic Pain Scale and the Symptom Checklist-90R (SCL-90R). Ulcers were photographed for measurement, and subjects rated pain levels on a 0-to-10 scale before and after swabbing of the ulcer with a saturated solution of sodium chloride and distilled water.* ***Results:*** *Mean characteristic pain intensity was 4.76, with a pain-related interference score of 1.21. None of the average SCL-90R subscale scores were considered elevated. In the model predicting pain intensity after swabbing, pain intensity before swabbing explained 43.6% of the variance (*P = *.000). Neither the addition of physical characteristics (*R^2 *change = .04;* P = *.28) nor psychologic characteristics (*R^2 *change = .09;* P = *.83) contributed significantly to the model. In contrast, only psychologic characteristics contributed to the variance explained in the model predicting pain-related interference (*R^2 *change = .505;* P = *.007).* ***Conclusions:*** *RAU is a moderately painful condition causing some impairment in functioning. Self-reported pain intensity of a sore does not appear to be influenced by psychologic characteristics. However, pain-related interference appears to be related to psychologic and not physical characteristics.* J OROFAC PAIN 2007;21:99–106

Key words: pain, psychology, recurrent aphthous ulcers

Recurrent aphthous ulcers (RAU), commonly referred to as canker sores, are a pervasive condition in which ovoid or round ulcers occur on the oral mucosa. The lesions, which are often painful, have a shallow necrotic center and are surrounded by raised margins and erythematous haloes.[1] RAU affect approximately 20% of the US adult population,[2] with a point prevalence of 0.89%, making it the 13th most common type of mucosal lesion in the United States.[3] The point prevalence of RAU in other adult populations has been reported to be as high as 2%.[4] Onset of RAU typically occurs in childhood, with a point prevalence of 1.64% in US children between the ages of 2 and 17.[5]

The etiology of RAU has not been definitively established, but is likely multifactorial. There appears to be a strong genetic compo-

nent, with 42% of patients with RAU having at least 1 first-degree relative with the condition.[6] When both parents have a history of RAU, the likelihood of developing the condition in offspring increases to 90%.[7,8] RAU has been associated with bacterial and viral infections[9] as well as trauma,[1] stress,[10] and diet.[11]

A psychological component to the etiology of RAU was proposed more than 30 years ago.[12,13] Since that time, numerous studies[10,14–16] have attempted to describe the psychologic characteristics of patients with RAU and the relationship between RAU and psychopathological characteristics. For example, Minneman and colleagues[14] assessed 217 recruits during basic combat training on personality measures of psychoticism, extroversion, introversion, and neuroticism and examined them for soft tissue oral pathology before and after combat training. Their data supported a relationship between personality traits and soft tissue pathology in recruits with extreme personality characteristics. Other authors have found elevations in general levels of anxiety and depression in subjects with RAU when compared to normal controls.[15,16]

Several authors[1,17,18] have suggested that anxiety and the physiologic response to stress may play a role in the etiology and maintenance of RAU. McCartan and colleagues[18] measured anxiety and salivary cortisol levels in 2 groups of patients. One group had persistent aphthae, and the other had been relieved of their aphthae following correction of hematinic deficiency. Those with persistent aphthae had higher levels of anxiety and elevated salivary cortisol levels when compared to those with resolved aphthae. These authors concluded that stress may play a role in the etiology of RAU, particularly in patients with an underlying anxiety disorder.

Chiappelli and Cajulis[17] suggested that the research supports a psychosomatic component to the etiology and prognosis of RAU but noted that the field remains controversial. An evaluation of the studies finding psychological differences suggested that conclusions are typically based on comparisons of RAU patients to normal controls or of RAU patients with active ulcers to those without ulcers. An examination of objective scores on a psychometric instrument with published norms would indicate whether or not this population displays significant psychopathology.

The research on nearly every other chronic pain condition focuses not only on pain severity but also on the impact of pain on normal levels of functioning (ie, disability and dysfunctional pain behaviors). These 2 aspects of pain are correlated but not redundant, and description of pain along these 2 axes has led to a better understanding of the multidimensional nature of chronic pain and the associated impact of pain on quality of life.[19] Given that many chronic pain conditions are refractory to treatment, examination of pain-related interference also allows for a better description of the predictors of disability and identification of other factors that are amenable to treatment interventions.

Although RAU has been defined as 1 of the most painful oral mucosal inflammatory conditions,[1] the clinical characteristics of the pain and the levels of pain-related interference due to RAU have not been reported. Sound epidemiological evidence for the clinical pain characteristics of RAU is needed to avoid "low level of evidence" assumptions based on case-series reports or clinical experiences. The aims of this study were *(1)* to use psychometrically sound measures to characterize the pain levels and pain-related interference associated with RAU; *(2)* to determine whether subjects with RAU report clinically significant psychologic symptoms; and *(3)* to examine the relationships between physical characteristics and self-reported psychologic symptoms, pain, and pain-related interference.

Materials and Methods

Participants

All subject selection, recruitment, and experimental procedures were approved by the University of Washington Institutional Review Board. Subjects were recruited through advertisements and flyers within the University of Washington community and by public service announcements. To be included in the study, subjects needed to be 18 years old, to have self-reported RAU, and to have an active ulcer that was less than 36 hours old. The natural history of healing time for RAU is still unclear, but most studies suggest that ulcers are at their most painful within the first few days of appearance and heal within 7 days. The determination to restrict subjects to lesions less than 36 hours old was made in order to have a sample of individuals with sores at the height of their pain and before the occurrence of healing.[20,21] An earlier cutoff time (eg, less than 24 hours old) would have resulted in an insufficient sample size. The criteria used may have led to a more acutely distressed sample, but one the present authors believe was still representative of RAU sufferers with persistent pain from RAU. Individuals were excluded

if they reported current use of tobacco products, anti-inflammatory drugs, antibiotics, or medication for RAU; had been previously diagnosed with Behçet syndrome, Sjögren syndrome, immune disorder (eg, lupus), or infectious disease (eg, human immunodeficiency virus, herpes); were currently undergoing radiation treatment; or were currently pregnant or trying to conceive.

Screening and Experimental Session

Subjects were instructed to contact the research study coordinator as soon as they noticed the first signs of an aphthous ulcer and were then immediately scheduled for their screening session. At the screening session, written informed consent was obtained. Subjects then completed a demographic questionnaire and a questionnaire developed for this study describing the characteristics (eg, onset, duration, frequency, and precipitating factors) of the RAU. Subjects also completed the Graded Chronic Pain Scale (GCPS)[22] and the Symptom Checklist-90R (SCL-90R).[23] If the subject had a sore that was less than 36 hours old, he or she was then examined by an oral medicine specialist. The specialist confirmed the diagnosis of at least 1 RAU and assessed the patient for any other mucosal diseases that might exclude the patient from participation. Subjects then underwent the experimental protocol. If the ulcer was more than 36 hours old, subjects were asked to call the coordinator immediately upon occurrence of a new ulcer. Since some subjects did not return, the sample is not a true sample of consecutively presenting patients. If mucosal ulcerative diseases could be ruled out, the oral medicine specialist diagnosed RAU based on a history of recurrence and the classic appearance of shallow, round-to-oval ulcerations with a characteristic halo.[2]

Experimental Sessions

At the experimental session, a registered dental hygienist (RDH) photographed the RAU with a fixed-focal-length camera to determine the dimensions of the ulcer and halo around the ulcer. A periodontal probe (PCPUNC15) was held in close proximity to the ulcer being photographed. The RDH asked the subject to rate baseline pain levels on a 0-to-10 scale (0 = no pain, 10 = pain as bad as could be) and then swabbed the RAU with a saturated solution of sodium chloride and distilled water. The subject then completed another 0-to-10 scale to rate the pain with irritation. The pain stimulation methodology was used because many individuals with RAU report no or very little pain without stimulation, usually associated with eating. This paradigm approximated the type of mechanical and chemical stimulation associated with eating.

Measures

Pain Characteristics. Pain characteristics were measured using the GCPS,[19] a self-report instrument designed to provide a quantitative index for assessing the impact and severity of chronic pain. Characteristic pain intensity (CPI) is measured as the average of three 0-to-10 scales (present pain, worst pain, average pain). Pain-related interference with activities is measured by three 0-to-10 scales (daily activities, work/household, social/recreational/family) and number of lost activity days (days unable to go to work or school, attend to household responsibilities, etc) attributed to pain. The GCPS assigns the severity of the pain condition to 1 of 5 categories based on intensity of pain and severity of pain-related disability: A grade of 0 corresponds to no pain; grade I is defined as pain of low intensity, averaging less than 5.0 on a 10-point scale, and associated with little pain-related interference in daily living; grade II is defined as high-intensity pain, greater than 5.0 on a 10-point scale, with low amounts of pain-related interference. Grades III and IV are associated with increasing levels of pain-related psychosocial disability regardless of pain level. The validity and reliability of the GCPS have been assessed in large population surveys[22] and large clinical samples.[19,24]

Psychologic Characteristics. The psychologic characteristics of the sample were measured using the SCL-90R.[23] The SCL-90R is designed to assess current psychological symptom status. The measure yields 9 subscale scores each with internal consistency and test-retest reliability values between 0.77 to 0.90, and 0.78 to 0.90, respectively. The measure also yields the Global Severity Index (GSI), which combines information from all of the subscales and is widely used as a single indicator of global distress.[23]

Physical Characteristics. Each lesion was photographed at each visit, and a color print of each image was used for analysis. A periodontal probe was photographed adjacent to the ulcer to use for calibration of all measurements. A rater who was blind to all outcome measures outlined the white ulcerous part of the lesion and the halo surrounding the ulcer with a mechanical pencil with 0.5-mm medium lead. The long axis of an ellipse across each ulcer or halo was designated the major

Table 1 Percentage of Subjects at Each GCPS Pain Grade for Patients with RAU, Back Pain, Headache, and TMD Pain

Grade	Pain and interference	RAU (n = 47)	Headache* (n = 779)	TMD* (n = 397)	Back pain* (n = 1,213)	Population sample* (n = 803)
0	Pain free	0	0	0	0	42.3
I	Low-intensity pain, low interference	48.9	29.7	40.7	34.9	19.9
II	High-intensity pain, low interference	44.7	40.1	43.5	27.9	22.0
III	Moderate interference	4.3	20.2	10.5	20.0	13.1
IV	Severe interference	2.1	10.0	5.4	17.2	2.6

*Data from Von Korff et al (2001).[26] Reprinted with permission from publisher.

axis length of the ulcer or the halo. The length of each axis was measured with a digital caliper and corrected to the nearest half-millimeter against the image of the periodontal probe.

Statistical Analysis

Pearson product-moment correlations were used to examine the bivariate relationships between pain intensity, pain interference, physical characteristics of the ulcer, and psychologic characteristics. Two hierarchical linear regressions were performed to examine the extent of the association between pain intensity with an irritant application, pain interference, physical characteristics of the ulcer, and psychologic characteristics (eg, GSI scale from the SCL-90R). The first regression included pain intensity rating after the irritant was applied as the dependent variable. Pain intensity with irritant was used as the major dependent variable because it more accurately simulates actual pain with normal use experienced by RAU sufferers. Physical characteristics of the sore (eg, its major and minor axes) and psychologic characteristics were entered sequentially as independent variables. The second regression included pain-related interference as the dependent variable and physical and psychologic characteristics as independent variables. All regressions were performed controlling for pain intensity of the sore before any irritant was applied and then physical characteristics. This order of factors was chosen (eg, baseline pain, physical characteristics, psychologic characteristics) in order to parse out the effects of physical factors before examining the role of psychologic factors. The subscales of the SCL-90R were highly intercorrelated, which could have led to problems with multicollinearity; thus only the proportion of variance accounted for by each independent variable group was examined rather than individual regression coefficients.[25] All analyses were performed with SPSS version 11.5.

Results

Baseline Characteristics

Forty-seven subjects (31 women, 16 men) participated in the study. The average age of subjects was 30.5 years (SD 12.7). Thirty-seven subjects (78.7%) identified their race as Caucasian, 9 (19.2%) as Asian, and 1 (2.1%) as African American. Twenty-seven subjects were never married, 16 subjects were married or living as married, and 4 were widowed or divorced. The sample was highly educated, with 31 subjects reporting 16 years or more of education. Average duration for experiencing RAU was 18.1 years (SD 10.1). Twenty subjects (42.6%) had seen a physician, dentist, or other health professional specifically for RAU treatment.

Self-Reports of Pain and Pain-Related Interference

The mean CPI score was 4.76 (SD 1.76). RAU pain had interfered with usual daily activities on a mean of 7.97 days (SD 15.62) of the last 180 days, and mean interference score was 1.21 (SD 1.68). Table 1 presents the percentage of subjects with

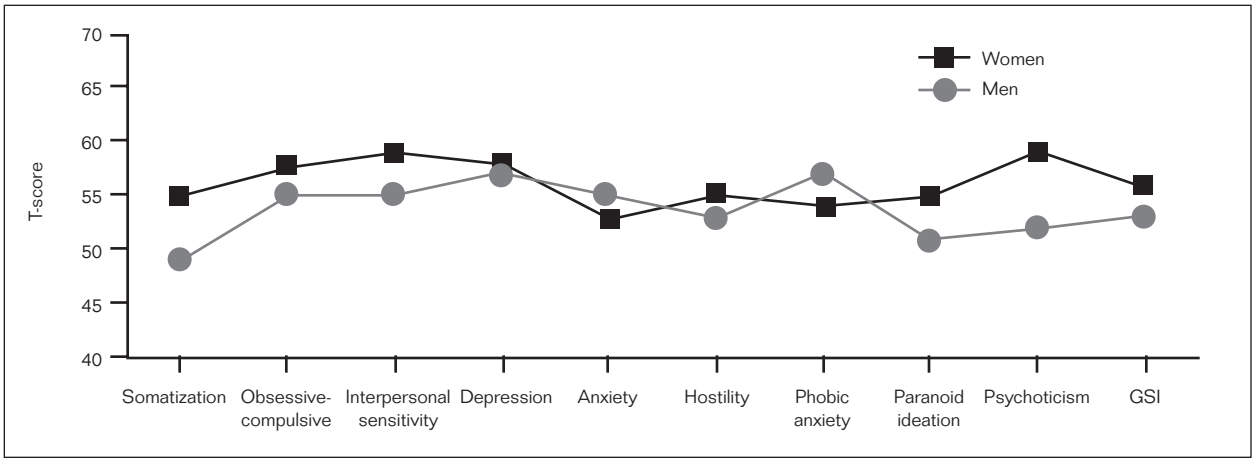

Fig 1 SCL-90R Profile for RAU subjects. Average T-scores are shown.

RAU pain in each GCPS classification compared with other chronic pain conditions and a community-based sample.[26]

Psychologic Characteristics of RAU Sample

SCL-90R raw scores were converted to standardized T-scores based on norms for adults (ie, nonpatients). The average T-scores for the primary symptom dimensions and the GSI are presented in Fig 1. Derogatis[23] suggested a decision rule of T-score ≥ 63 to define cases at a positive risk for psychiatric disorders. Overall, none of the average T-scores in the present sample were greater than 60. However, 32% (4 men, 11 women) of the 47 subjects had individual scale scores equal to or greater than a T-score cutoff of 63. There were no consistent patterns of scale elevations that would indicate any single type of psychological distress, and the GSI was also in the normal range. As would be expected, the 15 subjects with elevated scores on at least 1 individual scale typically exhibited higher scores in the neurotic subscales of obsessive-compulsive, interpersonal sensitivity, anxiety, and depression.

Relationship Between Pain Intensity, Pain-Related Interference, Physical and Psychologic Characteristics

Table 2 presents the bivariate correlations between pain intensity before swabbing with an irritant solution, after swabbing, pain-related interference, ulcer size, and psychologic characteristics. Table 3 presents 2 hierarchical linear regression analyses. In these analyses, pain intensity after swabbing and pain interference were the dependent variables. Pain intensity before swabbing, ulcer size, and psychologic characteristics (the GSI scale of the SCL-90R) were independent variables. The full model predicting pain intensity after irritation explained 47.7% of the variance ($P < .01$), but only pain intensity before swabbing contributed to the model (change in $F_{(1,36)} = 27.87$, $P < .01$). In contrast, the full model predicting pain-related interference explained 35.3% of the variance ($P < .01$). Neither pain intensity before swabbing nor physical characteristics of the ulcer explained significant proportions of the variance in pain-related interference. Only the addition of psychologic characteristics contributed significantly to the model (change in $F_{(1,33)} = 13.59$, $P < .01$).

Discussion

When there is a lack of accurate information about a physical ailment, distorted heuristic judgments of the frequency and severity of the condition may differ from actual base rates.[27,28] Therefore it is necessary that health-care professionals have precise data about a condition in order to best assist their patients in coping with it. The findings of this study suggest that RAU is a moderately painful condition that causes some impairment in functioning. The GCPS[19] was used to classify pain and pain-related interference to compare RAU sufferers to those with other chronic pain conditions.[26] The results suggest that, compared to previously reported pain-related characteristics for patients

Table 2 Bivariate Correlations Between Dependent and Independent Variables

	Dependent variables	
Independent variables	**Pain after swabbing**	**Pain-related interference**
Pain before swabbing	0.661*	0.033
Pain after swabbing	-	0.202
Pain-related interference	0.202	-
Major axis of ulcer	0.378*	0.142
Minor axis of ulcer	0.333*	0.261
Somatization	0.067	0.224
Obsessive-compulsive	0.084	0.571*
Interpersonal sensitivity	0.137	0.617*
Depression	0.111	0.607*
Anxiety	0.045	0.367*
Hostility	0.044	0.605*
Phobic anxiety	0.042	0.541*
Paranoid ideation	0.055	0.344*
Psychoticism	0.047	0.552*
GSI	0.095	0.571*

Table 3 Hierarchical Linear Regression Analysis with Pain Before Swabbing, Ulcer Size, and Psychologic Characteristics (SCL-90R Subscales) as Independent Variables

Measure	**R^2 (%)**	**R^2 change (%)**	**P‡**
Pain intensity after swabbing*			
Pain intensity before swabbing	43.6	43.6	.000
Physical characteristics	47.7	4.1	.280
Psychologic characteristics	47.7	0.0	.902
Pain-related interference†			
Pain intensity before swabbing	0.1	0.1	.844
Physical characteristics	8.6	8.5	.220
Psychologic characteristics	35.3	26.7	.001

*Adjusted $R^2 = 0.414$, $F_{(4,37)} = 7.53$, $P < .01$. Adjusted R^2 for full model.
†Adjusted $R^2 = 0.274$, $F_{(4,37)} = 4.50$, $P < .01$. Adjusted R^2 for full model.
‡R^2 versus R^2 change.

with other chronic pain conditions, subjects with RAU have slightly less intense pain and interference than chronic TMD sufferers. Although RAU pain is relatively brief, episodic, and less disabling in comparison to other pain conditions, these findings suggest significant amounts of pain and pain-related suffering among those experiencing RAU. The degree of pain and pain-related interference experienced by subjects in this sample was of sufficient intensity that more than 40% of the sample had previously sought treatment.

The question of whether psychologic stress or psychopathologic states contribute to RAU outbreaks has been the subject of considerable debate. Some studies suggest no relationship between stress and outbreak[10]; others have found a relationship between stress and outbreak or a higher incidence of pathologic anxiety and other psychologic dysfunction in those with RAU.[15,16,18] The results of the present study suggest that RAU sufferers have no more psychologic distress than would be found in a normal nonpatient population. This study compared a sample of those with RAU to a clinical

standard using an established, psychometrically valid instrument. The differences in methodology between this study and others may account for the difference in outcome. Other studies had small sample sizes[15] or compared anxiety scores and other psychologic measures of patients with an active ulcer either to patients with a treated ulcer[18] or to a sample of normal, pain-free subjects.[16] In the future, researchers investigating whether those with RAU have a higher incidence of psychopathology may wish to combine structured psychiatric interviews with self-report measures.

Although the present data do not suggest that those with RAU have greater psychologic distress, they do illuminate several important issues related to the nature of the relationship between physical findings, psychologic characteristics, pain intensity, and pain-related interference with normal activities. Pain intensity associated with a sore appears to be predominantly related to physical characteristics. Bivariate correlations suggested that pain intensity after an irritant was applied to the ulcer was associated with the size of the ulcer and with pain levels prior to any irritation. Multivariate analyses suggested that the nature of the association was primarily due to pain levels prior to any irritation.

In contrast, the level of self-reported interference with normal activities did not appear to be related to pain intensity or physical characteristics of the ulcer but instead to psychologic characteristics. Bivariate and multivariate analyses suggested that the nature of that association was predominantly psychologic. Particularly, the psychologic characteristics of high interpersonal sensitivity, depression, and hostility were significantly and positively associated with RAU pain-related interference. This is consistent with the literature on other chronic pain conditions, including cancer,[29,30] spinal cord injury,[31] and TMD pain.[32,33]

The implication for health professionals treating RAU is that they will best serve their patients by adoption of a biopsychosocial model for RAU sufferers. While pain levels are an important aspect in determining the significance and problematic nature of any ailment, treatment could be improved not only by assessing pain levels but also by learning more about their patients as individuals and asking, either in the context of the interview or via a self-report questionnaire, about the level of RAU-related interference with normal activities. This is important because pain level alone is not the sole factor producing the degree of disturbance in a patient's life; rather, psychologic factors contribute to the degree that the condition interferes with daily functioning.

This study has several important limitations. First, although a large proportion of the sample had sought treatment for RAU, subjects were recruited within the university community rather than within a clinic population. As such, these findings may not generalize to those who seek treatment for RAU. Further, this study compared pain characteristics and psychologic profiles of those with RAU to established norms rather than to a matched control group and used only self-report instruments to evaluate pain, pain interference, and psychologic characteristics. This is an important early step in the determination of the pain and psychosocial profile of a population, but future studies could benefit from more rigorous psychophysiologic testing of pain sensitivity and tolerance and structured interviewing to determine psychologic profiles. Furthermore, the main outcome measure in the present study, the GCPS, was developed for pain conditions such as back, headache, and facial pain. The GCPS provided a brief, easily administered assessment of pain-related interference and might be a practical adjunct to clinical assessment. However, since the GCPS examines interference with recreational and work-related activities, it may be too blunt a measure to provide a full assessment of RAU pain-related interference. Other measures more suited to facial pain, such as the Jaw Function Limitation Scale,[34] may be better adapted for this condition, and future research should include an examination of valid and reliable instruments for the measurement of RAU pain limitations.

RAU is 1 of the most common mucosal lesions in the United States,[3] yet there are few effective treatments[1] and a dearth of extant research characterizing this patient population. Thus, health-care professionals may tend to underestimate the problem and its severity, and this could adversely impact the attention and care sufferers receive. Our findings suggest that, in fact, RAU results in considerable pain and pain-related interference and that attention to both biologic and psychosocial factors could improve our understanding and treatment of the condition.

Acknowledgments

This research was supported by National Institute of Dental and Craniofacial Research grant no. R41 DE015740.

References

1. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis. J Am Dent Assoc 2003;134:200–207.
2. Langlais RP, Miller CS. Color Atlas of Common Oral Diseases, ed 2. Philadelphia: Lippincott Williams & Wilkins, 1998.
3. Shulman JD, Beach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in US adults: Data from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Dent Assoc 2004;135:1279–1286.
4. Axell T. A prevalence study of oral mucosal lesions in an adult Swedish population. Odont Rev 1976;27:1–103.
5. Shulman JD. An exploration of paint, annual, and lifetime prevalence in characterizing recurrent aphthous stomatitis in USA children and youths. J Oral Pathol Med 2004; 33:558–566.
6. Shohat-Zabarski R, Kalderon S, Klein T, Weinberger A. Close association of HLA-B51 in persons with recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1992;74:455–458.
7. Ship II. Inheritance of aphthous ulcers of the mouth. J Dent Res 1965;44:837–844.
8. Ship II. Epidemiologic aspects of recurrent aphthous ulcerations. Oral Surg Oral Med Oral Pathol 1972;33: 400–406.
9. Elsheikh MN, Mahfouz ME. Prevalence of helicobacter pylori DNA in recurrent aphthous ulcerations in mucosa-associated lymphoid tissues of the pharynx. Arch Otolaryngol Head Neck Surg 2005;131:804–808.
10. Pederson A. Psychologic stress and recurrent aphthous ulceration. J Oral Pathol Med 1989;18:119–122.
11. Nolan A, Lamey PJ, Milligan KA, Forsyth A. Recurrent aphthous ulceration and food sensitivity. J Oral Pathol Med 1991;20:473–475.
12. Harris M. Psychosomatic disorder of the mouth and face. Practitioner 1975;214:372–379.
13. Larato DC. Stress and aphthous ulcers. J Acad Gen Dent 1972;20:25–26.
14. Minneman MA, Cobb C, Soriano F, Burns S, Schuchman L. Relationships of personality traits and stress to gingival status or soft-tissue oral pathology: An exploratory study. J Public Health Dent 1995;55:22–27.
15. Soto Araya M, Rojas Alcayaga G, Esguep A. Association between psychological disorders and the presence of oral lichen planus, burning mouth syndrome, and recurrent aphthous stomatitis. Med Oral 2004;9:1–7.
16. Tang L, Ma L, Liu N. Effects of psychosocial factors on recurrent aphthous ulcer. [abstract]. Hua Xi Kou Qiang Yi Xue Za Zhi 2001;19:102–103.
17. Chiappelli F, Cajulis OS. Psychobiologic views on stress related oral ulcers. Quintessence Int 2004;35:223–227.
18. McCartan BE, Lamey PJ, Wallace AM. Salivary cortisol and anxiety in recurrent aphthous stomatitis. J Oral Pathol Med 1996;25:357–359.
19. Von Korff M, Dworkin SF, LeResche L. Graded chronic pain status: An epidemiologic evaluation. Pain 1990;40: 279–291.
20. Arikan OK, Birol A, Tuncez F, Erkek E, Koc C. A prospective randomized controlled trial to determine if cryotherapy can reduce the pain of patients with minor form of recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e1–e5.
21. Alidaee MR, Taheri A, Mansoori P, Ghodsi SZ. Silver nitrate cautery in aphthous stomatitis: A randomized controlled trial. Br J Dermatol 2005;153:521–525.
22. Von Korff M, Ormell J, Keefe F, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133–149.
23. Derogatis LR. Symptom Checklist 90-R. Minneapolis, MN: National Computer Systems, 1991.
24. Dworkin SF, Sherman JJ, 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;16:207–220.
25. Myers JL, Well AD. Research Design and Statistical Analysis. New York: HarperCollins, 1991.
26. Von Korff M. Epidemiological and survey methods: Assessment of chronic pain. In Turk DC, Melzack R (eds). Handbook of Pain Assessment. New York: The Guilford Press, 2001:603–618.
27. Kahneman D, Tversky A. On the psychology of prediction. Psychol Rev 1973;80:237–251.
28. Kahneman D, Tversky A. The psychology of preferences. Sci Am 1982;246:160–173.
29. Schulz-Kinderman F, Hennings U, Ramm G, Zander AR, Hasenbring M. The role for biomedical and psychosocial factors for the prediction of pain and distress in patients undergoing high-dose therapy and BMT/PBSCT. Bone Marrow Transplant 2002;29:341–351.
30. Syrjala KL, Chapko ME. Evidence for a biopsychosocial model of cancer treatment-related pain. Pain 1995;61: 69–79.
31. Putzke JD, Richards JS, Hicken BL, DeVivo MJ. Interference due to pain following spinal cord injury: Important predictors and impact on quality of life. Pain 2002;100:231–242.
32. Brown FF, Robinson ME, Riley JL, Gremillion HA. Pain severity, negative affect, and microstressers as predictors of life interference in TMD patients. Cranio 1996;14: 63–70.
33. 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.
34. List T, Paulin G, Lundstrom I, Ohrbach R. Orofacial disorder diagnosis: Relationship to the jaw limitation scale. J Dent Res (Special Issue A)2002;81:1024.