Experimental Gingivitis in Male Khat (*Catha edulis*) Chewers

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Abstract

Whether or not khat chewing is detrimental to the periodontium remains uncertain. Findings from cross-sectional studies have been contradictory and, in most cases, uncontrolled for confounders. **Objectives**: to experimentally test the effect of khat chewing on formation of dental plaque and development of gingivitis. **Methods:** This was a split-mouth, parallel-group, 20-day experimental gingivitis study involving non-smoking, young, male khat chewers (n = 8) and non-chewers (n = 9). Measurements of plaque index (PI), gingival index (GI), and bleeding on probing (BOP), as experimental outcomes, were performed on days 0, 10, and 20. Scores were compared between the two groups (parallel-group model) and between the khat-chewing and non-chewing sides (split-mouth model). **Results:** All experimental outcomes significantly increased over time. Results from the two models were consistent. Khat chewing was associated with lower PI scores; however, differences were only significant at day 20. Despite scoring higher in baseline gingival inflammation, the khat chewers and khat-chewing sides showed significantly lower GI and BOP scores at days 10 and 20. The effect of khat chewing was evident on both the lingual and buccal aspects. **Conclusions:** The observed anti-plaque and anti-gingivitis properties indicate that khat chewing is probably not detrimental to the periodontium. The validity of previous findings supporting an opposite view is undermined by lack of control for confounders, particularly smoking.

Key words: Catha edulis; dental plaque; khat; gingivitis; periodontitis

Introduction

Khat, or *Catha edulis*, is an evergreen shrub of the plant family *Celastraceae* indigenous to Yemen and East Africa, where a high proportion of the population habitually chews its fresh leaves and twigs for their amphetamine-like effects (Kalix, 1996). The habit remained confined to these geographical areas for centuries; however, it has recently spread to Western countries by immigrants, becoming of more interest to the international scientific community (Nencini *et al.*, 1989; Browne, 1991; Tacke *et al.*, 1992; Al-Samarraie *et al.*, 2007). Comprehensive information about the history, botany, production, geographical distribution, chemistry and pharmacology of khat, and the social, economic, medical, psychological, and oral aspects of its use is provided in recent reviews (Al-Motarreb *et al.*, 2002; Al-hebshi and Skaug, 2005b). In general, much of the claims about the adverse health effects of khat chewing are either anecdotal or based on inadequate evidence (Kennedy *et al.*, 1987; Al-hebshi and Skaug, 2005b).

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Khat is usually chewed into a large bolus that is kept in one side of the mouth for several hours, which raises a clinically relevant question about the effect of this habit on periodontal health. Unfortunately, existing literature doesn't provide a clear view on this matter. Comparative cross-sectional clinical studies have reported conflicting results (Hill and Gibson, 1987; Jorgensen and Kaimenyi, 1990; Mengel *et al.*, 1996; Al-akhali , 2002; Al-sharabi, 2002; Ali, 2007); while comparisons between chewers and non-chewers indicate that khat chewing is detrimental to the periodontium, comparisons between khat-chewing and non-chewing sides suggest the opposite. Notably, none of these studies controlled for important confounders such as smoking and oral hygiene, which renders interpretation of the findings unreliable. At the microbial level, khat has been shown to possess selective antimicrobial properties and to induce microbial shifts in dental biofilm that are not incompatible with periodontal health (Al-hebshi, 2005; Al-hebshi and Skaug, 2005a; Al-hebshi *et al.*, 2006), supporting the view that khat may not be detrimental to the periodontium. Obviously, a sound conclusion cannot be made before controlled, longitudinal *in vivo* studies are carried out to evaluate the effect of khat chewing on microbial and clinical periodontal parameters. Therefore, the purpose

of the current study was to experimentally test the effect of khat chewing on formation of dental plaque and development of gingivitis *in vivo*.

Materials and methods

Experimental subjects

Sample size calculation was made using the formula for normally distributed means (Fliess, 1992) with the aim of detecting a clinically significant difference (> 20% difference) in mean gingival index (primary outcome), given a β value of 0.10 (90% power), an α level of 0.05, and a SD of 0.15. Accordingly, a sample size of nine was planned.

Nine male khat chewers (22-28 years old) and nine male khat non-chewers (21-23 years old), who fulfilled inclusion criteria and gave consent, were recruited from among dental students at the Faculty of Dentistry, University of Science and Technology, Sana'a, Yemen. A khat chewer was defined as a person who chewed khat at least four days per week, for at least four hours per day. A subject was excluded if there was evidence of 1) periodontitis, 2) use of any form of tobacco, 3) extensive prosthodontic work, and 4) any systemic disease known to modify periodontal reaction to dental plaque.

Study design

This was a 25-day prospective, longitudinal, experimental gingivitis study, a modification of the original study by Loe and Holm-Pedersen (1965). The study combined two models to test the effect of khat chewing on plaque formation and gingival inflammation: a parallel-group model in which khat chewers and non-chewers were compared (inter-group comparison), and a split-mouth model in which khat chewing sides and khat non-chewing sides were compared (intra-group comparison).

The study subjects first received a professional full-mouth dental prophylaxis, and were provided with a 0.12% chlorhexidine mouth wash (Hexadyl, Saba pharma, Yemen) and asked to use it twice daily (every 12 hours) for five successive days. The purpose of this five-day hygienic phase was to bring plaque and gingival health to baseline. The subjects then entered a 20-day experimental phase during which they refrained from all measures of oral hygiene to allow for uninterrupted build-up of plaque and development of gingivitis. The khat chewers were directed to follow their habit routine during the 25-day period. Measurements of experimental outcomes were made at day 0 (baseline), day 10, and day 20 of the experimental phase.

The study was approved by the faculty board after addressing ethical considerations. All study subjects gave informed verbal consent.

Experimental outcomes

Plaque formation and gingival inflammation (experimental outcomes) were assessed using the plaque index (PI) (Silness and Loe, 1964), gingival index (GI) (Loe and Silness, 1963), and bleeding on probing (BOP) expressed as % sites with bleeding. Measurements were made at six sites per tooth for all teeth except third molars; teeth with a restoration reaching the gingival margin were excluded. All measurements were performed by a single calibrated examiner (Al-ak'hali MS). Although participants were interviewed by a person other than the examiner, complete blinding of the examiner to the khat chewing status of the subjects was not possible because some khat chewers could be identified by the presence of khat remnants between the teeth.

Statistical analysis

Eight khat chewers (one subject dropped out) and nine khat non-chewers were included in the analysis. PI, GI and BOP scores were calculated for each subject (analysis unit of inter-group comparisons), and among the chewers, for the chewing and non-chewing sides separately (half-mouth scores; analysis unit of intra-group comparisons). Descriptive statistics (means and standard deviations) were calculated for the study population and each subject/side group. The significance of differences in experimental outcomes scores in the study population at the successive time points were determined using the Friedman test; for significant differences, multiple comparisons were made using the Wilcoxon signed rank test. The latter test was also used to assess significance of differences in scores between the khat-chewing and non-chewing sides at each time point. The significance of differences between the khat chewers and non-chewers was sought using the Mann-Whitney test. *P* values ≤ 0.05 were considered statistically significant. In multiple comparisons, this value was divided by the number of comparisons made. All analyses were performed using SPSS 12.

Results

General findings – the model

Seventeen males, 21-28 years old, completed the study. The khat chewers were slightly older, but the difference was statistically insignificant. The frequency and duration of khat chewing ranged between 4-7 days/week and 4-6 hours/day, respectively. Seven of the eight chewers exclusively used their left side for chewing (87.5%).

The mean PI, GI, and BOP scores in the study population at the different time points are presented in Table 1. As expected, all parameters significantly increased over the course of the experimental phase ($p \leq 0.0001$). PI scores strongly correlated with both GI and BOP scores ($R^2 = 0.82$ and 0.73, respectively).

Table 1. Experimental outcomes scores (mean ± SD) in the study population (n = 17) at baseline, 10 days, and 20 days after refraining from oral hygiene

	Baseline	10 days	20 days
Plaque index*	0.15 (0.08)	0.84 (0.16)	1.28 (0.27)
Gingival index*	0.25 (0.32)	1.20 (0.13)	1.28 (0.13)
Bleeding on probing (% sites bleeding)*	3.5 (5.2)	22.5 (10.9)	28.0 (12.0)

*$p \leq 0.0001$; Friedman test

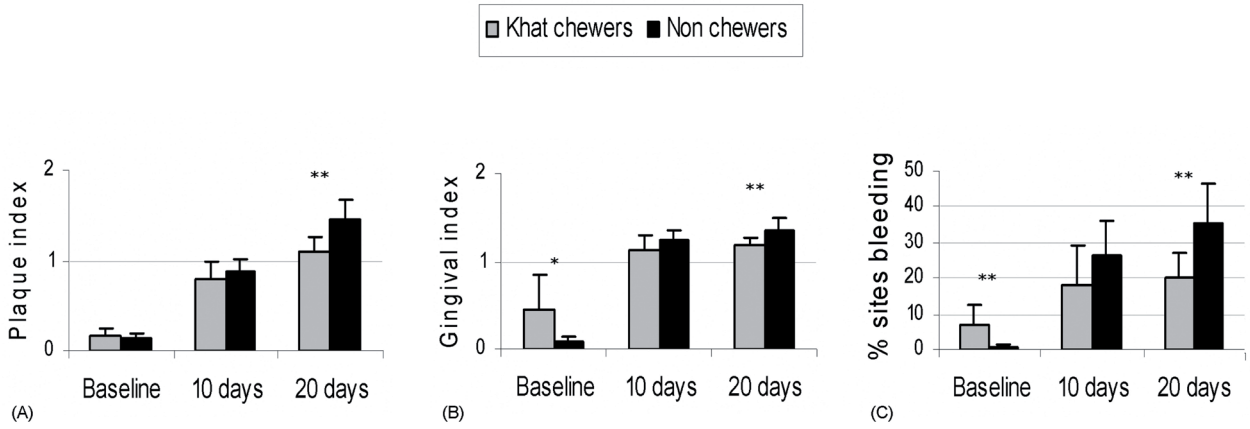

Figure 1. Clustered bars showing the mean and standard deviation of A) plaque index, B) gingival index, and C) bleeding on probing (% sites bleeding) scores in the khat chewers (n = 8) and non-chewers (n = 9) at baseline, 10 days, and 20 days after refraining from oral hygiene. *p ≤ 0.05 and **p ≤ 0.01; Mann-Whitney test.

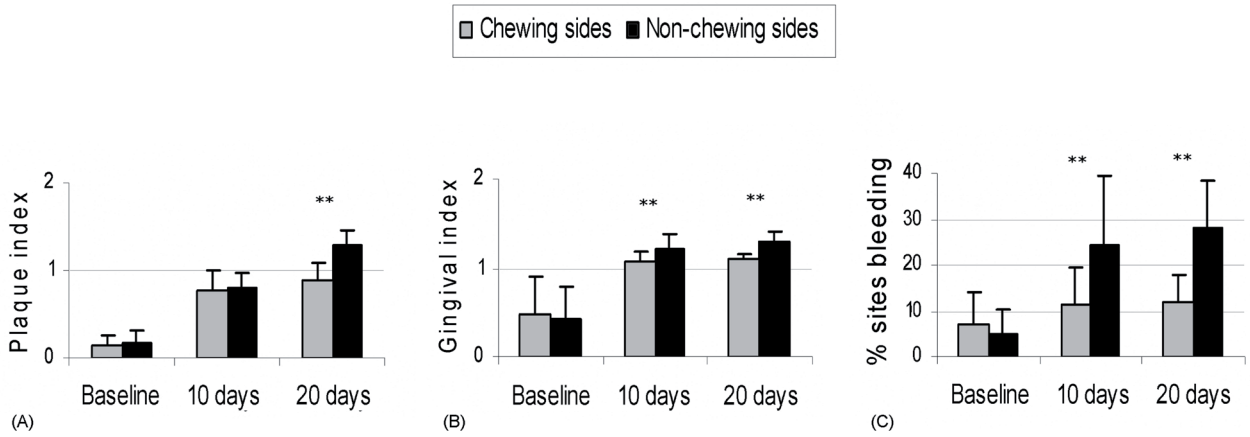

Figure 2. Clustered bars showing the mean and standard deviation of A) plaque index, B) gingival index, and C) bleeding on probing (% sites bleeding) scores in the khat chewing and non-chewing sides at baseline, 10 days, and 20 days after refraining from oral hygiene. **p ≤ 0.01; Wilcoxon signed rank test.

Multiple comparisons showed that increases in scores were significant for all parameters between day 0 and day 10 ($p \leq 0.001$), but only for PI between day 10 and day 20 ($p \leq 0.0001$).

Khat chewers vs. khat non-chewers (inter-group comparison)

Differences in experimental outcomes scores between the khat chewers and non-chewers are shown in Figure 1. At baseline, the khat chewers showed significantly higher GI and BOP scores than did the non-chewers ($p = 0.034$ and 0.01, respectively), although there was no significant difference in PI scores between the two groups. No significant differences were noted at day 10; however, the khat chewers tended to have lower scores of all outcomes. At day 20, all experimental outcomes scores were significantly lower in the khat chewers than in the khat non-chewers ($p = 0.006$, 0.01, and 0.004 for PI, GI, and BOP, respectively).

Khat-chewing sides vs. khat non-chewing sides (intra-group comparison)

Figure 2 demonstrates the differences in experimental outcomes scores between the khat-chewing and non-chewing sides. In contrast with the findings above, the khat-chewing and non-chewing sides did not show significant differences in any parameter at baseline. At day 10, however, the khat chewing sides had significantly lower GI and BOP scores than did the non-chewing sides ($p = 0.01$), although PI scores did not significantly differ between the two sides. At day 20, all parameters were significantly lower on the khat-chewing sides than on the non-chewing sides ($p = 0.01$), which is consistent with differences between the khat chewers and non-chewers.

Further analyses of differences between the two study sides were performed taking the scores from the buccal and lingual aspects separately (Figure 3). The significant difference between the two sides in PI scores at day 20 noted above was only evident on the buccal aspect ($p = 0.01$). Differences in GI scores were significant on only the buccal aspect at day 10 ($p =0.02$), but on both the buccal and lingual aspects at day 20 ($p =0.01$ and 0.02, respectively). The significant differences in BOP scores between the two sides at day 10 and day 20 were found on both the buccal aspect ($p = 0.02$ and 0.04, respectively) and lingual aspect ($p = 0.01$ and 0.02, respectively).

Discussion

To the best of our knowledge, this is the first time that khat chewing was experimentally tested for its effect on clinical periodontal parameters *in vivo*. The study is in fact the latest in a series of studies that are aimed at resolving the existing controversies on the association between khat chewing and periodontal diseases. The experimental gingivitis model was first used to demonstrate the association between dental plaque accumulation and gingival inflammation (Loe and Holm-Pedersen, 1965). Since then, the model, with or without modifications, has been extensively used by researchers for different purposes, including evaluation of certain risk factors such as smoking (Salvi *et al.*, 2005) and oral contraceptives (Preshaw *et al.*, 2001), assessing the efficacy of oral mouth washes and antiplaque/antigingivitis agents (Archila *et al.*, 2005; Lorenz *et al.*, 2006; Albert-Kiszely *et al.*, 2007), and exploring mechanisms underlying gingival inflammation (Scapoli *et al.*, 2007). The model involves a comparison either between a test group and a control group (parallel-group model), or between test sides/quadrants and control sides/quadrants (split-mouth model). The current study combined both models to obtain more information and improve the validity of results and conclusions.

In a slight difference from the 21-day classic Loe's study, the experimental phase of the current study lasted 20 days and clinical assessment was carried at 10-day rather than 7-day intervals. Being unable to blind the study and the possibility of carry-over effects are, however, the main limitations of our study. Consequently, some measurement bias and underestimation of differences between the khat chewing and non-chewing sides cannot be totally excluded.

At baseline, the khat chewers showed significantly higher gingival inflammation scores than did the non-chewers, despite that PI scores were low and did not significantly differ between the two groups, indicating that the khat chewers were less responsive to the hygienic phase. This difference, however, is probably a residue of similar differences in gingival inflammation status between the two groups prior to the hygienic phase. Therefore, a longer hygienic phase was probably required.

As experimental gingivitis started to develop, the situation dramatically changed. The two experimental models consistently showed that khat chewing was strongly associated with lower scores of gingival inflammation at days 10 and 20, indicating that khat chewing may have anti-gingivitis properties. Interference with plaque accumulation was probably the main mechanism involved. However, both models demonstrated that differences in PI scores were only significant at day 20, suggesting that the observed anti-gingivitis properties of khat chewing cannot be entirely explained by its effect on plaque accumulation. It is very well known that gingivitis is not only associated with increases in plaque quantity, but also with shifts in its microbial composition from one dominated by Gram-positive cocci into another in which Gram-negative, anaerobic bacilli and spirochetes dominates (Carranza and Newman, 1996). It is, therefore, possible that khat chewing also positively

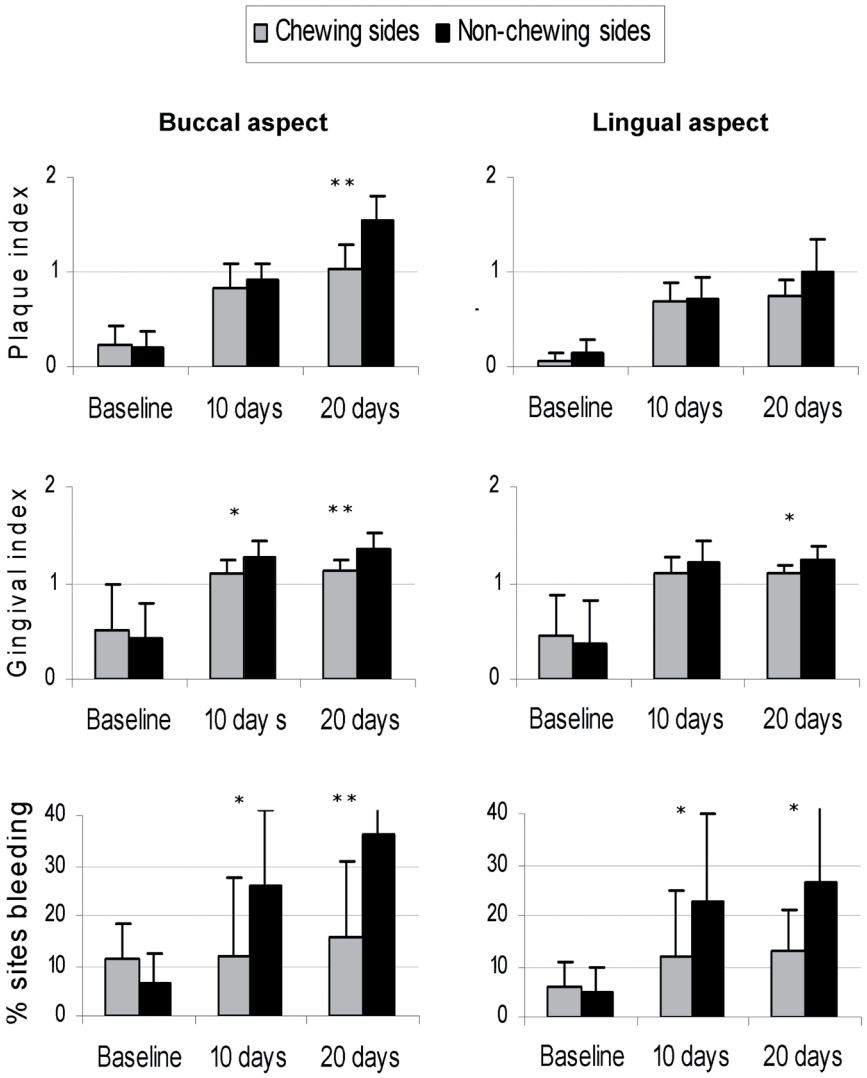

Figure 3. Clustered bars showing the means and standard deviations of experimental outcomes scores in the khat-chewing and non-chewing sides at baseline, 10 days, and 20 days, taking the buccal aspect (left) and lingual aspect (right) separately. *p ≤ 0.05 and **p ≤ 0.01; Wilcoxon signed rank test

influenced the composition of dental plaque, not only its quantity. In fact, aqueous khat extracts have previously been shown to possess selective antimicrobial properties *in vitro*, being particularly active against Gram-negative periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*, but largely inactive against Gram-positive, health-compatible species including streptococci and actinomyces (Al-hebshi, 2005; Al-hebshi *et al.*, 2006). In line with that, khat chewing has also been demonstrated to induce microbial shifts *in vivo* that are compatible with periodontal health (Al-hebshi and Skaug, 2005a).

To determine if the observed effects of khat chewing on the different parameters were chemically mediated or simply due to the mechanical action of the khat bolus, comparisons between the khat-chewing and non-chewing sides were performed for the buccal and lingual aspects separately. A purely mechanical action should have resulted in significant differences in parameters between the two sides on the buccal aspect only. However, this was not the case. Significant differences in gingival inflammation scores did exist on the lingual aspect; the differences existed in the absence of differences in PI scores, which further supports that khat possibly had a positive effect on composition of dental plaque. Significant differences in PI were only seen on the buccal aspect. In addition, the differences in gingival inflammation scores were greater on the buccal side, suggesting that khat chewing had a combined mechanical and chemical action on the buccal aspect, and only a chemical one lingually. In fact, a previous study found that khat chewers had lower lingual plaque and gingival inflammation scores than did khat non-chewers, supporting that at least part of the anti-gingivitis properties of khat are due to a chemical action.

Findings from the split-mouth model in the current study are largely consistent with those obtained from comparisons between khat-chewing and non-chewing sides in three previous cross-sectional studies (Hill and Gibson, 1987; Mengel *et al.*, 1996; Al-akhali, 2002), in which khat-chewing sides were shown to have significantly lower scores of periodontal parameters examined than did non-chewing sides. However, in total disagreement with findings from our parallel-group model, comparisons between the khat chewers and non-chewers in the same studies and two more (Al-sharabi, 2002; Ali, 2007) revealed opposite results, which is rather confusing. Such contradictions probably arose because previous researchers failed to properly adjust for the effect of smoking, which is also a habit for the majority of khat chewers. Smoking is an established risk factor of periodontitis; approximately half of periodontitis cases have been attributed to either current or former smoking and up to 90 percent of refractory periodontitis patients are smokers (Johnson and Slach, 2001). Therefore, differences in periodontal health between khat chewers and khat non-chewers observed in previous cross-sectional studies were probably due to smoking rather than khat chewing per se.

Experimental gingivitis studies allow for assessment of effects of a particular factor on only plaque accumulation and gingival inflammation. Periodontal parameters related to periodontitis such as clinical loss of attachment, pocket depth, and gingival recession represent chronic, slowly progressive irreversible processes, which for practical and ethical reasons cannot be induced experimentally; the effect of khat chewing on these can only be assessed through cohort or controlled, large scale cross-sectional studies. However, considerable evidence indicates that there is an association between susceptibility to gingivitis and susceptibility to periodontitis (Trombelli, 2004). Based on results from the current study one can, therefore, predict that khat chewing probably decreases susceptibility to periodontitis, which is also supported by results from some cross-sectional studies as described above.

In conclusion, overall evidence does not support that khat chewing per se is detrimental to periodontium. On the contrary, khat chewing seems to reduce gingival inflammation, interfere with plaque accumulation, and produce microbial shifts that are compatible with periodontal health. However, the majority of khat chewers are also smokers, which places them at great risk for not only periodontitis but also other serious health problems.

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Erratum notice

The publishers wish to apologise for the incorrect arrangement of authors name within the article entitled 'Clinical and Microbiological Effects of Adjunctive, Locally Delivered Chlorhexidine on Patients with Chronic Periodontitis' by D. Sakellari *et al.' Journal of the International Academy of Periodontology* 2010 **12**/1: 20-26.

The correct arrangement of names is as follows:

Clinical and Microbiological Effects of Adjunctive, Locally Delivered Chlorhexidine on Patients with Chronic Periodontitis

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