

Aus dem Bereich für Oralmedizin, zahnärztliche Röntgenologie und –
Chirurgie des CharitéCentrum für Zahn – Mund – und Kieferheilkunde
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Oral white lesions due to qat chewing among women in Yemen

zur Erlangung des akademischen Grades
Doctor medicinae dentariae (Dr. med. dent.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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Datum der Promotion: 08. April 2011

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1. INTRODUCTION

The qat plant (*Catha edulis* Forsk) is a small to large tree, which belongs to the family Celastraceae. This plant is grown in Yemen and some countries of East Africa including Ethiopia, Somalia, Kenya, Madagascar, and Tanzania.

The fresh leaves and young shoots of qat are habitually chewed for their amphetamine-like effect (1). The qat (Syn: Kaht, Khat, Quat, Qat, Mirra, etc) chewers start to chew the leaves one by one; the juice is swallowed and the chewed materials is kept in the buccal sulcus either unilaterally or bilaterally for several hours and later expectorated. This habit is practiced by several millions of peoples in Yemen and some countries of East Africa. Qat chewing habit is predominant among males however, recently it was reported that women start to chew qat as an integral part of their social life (2).

Chemical analyses found that there are three groups of alkaloids present in qat: phenylalkalamine, phenylpentalamine and cathedulins (3). Cathine and cathinone are the main constituents of qat that have amphetamine-like effects (1). Other components of qat including amino acids, vitamins, tannin and minerals were reported in different concentrations (4, 5, 6).

Qat has a negative aspect medically, psychologically, socially and economically. The qat syndrome is described by Kalix in 1988 as a combination of certain signs and symptoms as a result of CNS stimulation and sympathomimetic effects of qat (7). The symptoms of CNS stimulation including: increase in the level of energy, and alertness with improved ability to communicate. The side effects of qat include increase blood pressure, tachycardia, loss of appetite, insomnia and some gastrointestinal disturbances (8, 9, 10, 11).

Qat consumption may induce moderate psychic dependence on withdrawal. Symptoms include lethargy, mild depression, slight trembling and recurrent bad dreams (8). The adverse effects of qat chewing on oral health have been reported in some studies. These effects on hard tissues include attrition, staining and cervical caries (12). Regarding the oral soft tissues, certain changes such as keratosis and keratotic white lesion were significantly associated with qat chewing (12, 13, 14, 15, 16). Furthermore, some investigators found a significant correlation between frequent qat chewing and oral cancer (17, 18, 19, 20).

On the other hand, several studies failed to report any positive correlation between oral diseases and qat chewing (14, 21, 22). The conflicting results on the effects of qat

chewing on oral health need further studies with proper design and inclusion criteria aiming to further elaborate the exact effect of qat chewing on oral health.

In Yemeni population, only few studies were conducted among adult males to investigate the effect of qat chewing on the oral health. Because no previous studies were carried out on Yemeni women, the present study was conducted to assess the prevalence of oral white lesion and its potential correlation with qat chewing among Yemeni women.

1.1. Objectives of the study

1- To determine the presence of white lesion among Yemeni women

2- To assess the correlation between qat chewing and presence of white lesion among Yemeni women.

3- To assess the correlation between smoking, water pipe smoking and their duration and frequency with the presence of white lesion.

4- To assess the correlation between the duration and frequency of qat chewing with the presence of white lesion.

2. LITERATURE REVIEW

2.1. History of qat origin and use

Qat is a plant of species *Catha Edulis* Forsks, which belongs to the family Celastraceae. This plant is grown in some countries of East Africa including Ethiopia, Somalia, Kenya, Madagascar, Tanzania, and South countries of Arabia, including south-west of Saudi Arabia and Yemen Republic. Little information is available regarding the qat mainland whether it was Ethiopia or Yemen (23). It appears that qat was first used by Ethiopians for recreation as documented by their chronicle written in the 14th century (24). It was also probable that qat was first introduced to Yemen in the 15th century where it was used in a form of a drink of dry leaves among the Sufis during their religious ceremonies (21). The drink was weak compared to coffee, and then qat use was modified by chewing its leaves and absorbing its ingredients (25). By the middle of the 16th century, qat use was common among the upper class only. Because qat alters the mood to one's expectations, the opinion of religion was sought (23). The first religion opinion provided by the famous Islamic scholar Hythemi stated that qat is different from alcohol or opium and should not be prohibited. Thus, use of qat continued to spread among all classes of Yemenis during 17th, 18th to 19th centuries (2, 23). In the early 20th century, the use of qat became wider and was consumed by all social strata. It was expensive and remained occasional for most of the society. In the 1970s, qat use exploded in Yemen. By the end of the 20th century, qat use became prevalent all over the country and in men and women (26). Accordingly, qat production has increased significantly during the last three decades of the 20th century partially replacing other crops, mostly grapes and coffee. In thousands of tons, qat production increased from 76.1 in 1991 to 108 in 2000 (27).

2.2. Qat prevalence

Several studies were carried out among Yemeni population to determine the prevalence of qat chewing habit among males and females. The results of these studies revealed that the prevalence of qat chewing habit ranged from 60% to 90% in males and from 10% to 77% in females. In 1967, it was reported that 60% of males and 35% females were qat users (20). In 1972, 80% of adult men in cities and 90% of adult men in villages were regular qat chewers (28). In 1976, research work was carried out in the region of Aden. Authors estimated that 50% of the male adult population were qat

chewers (29). In mid-1980, Kennedy reported that 80-85% of men and 50-60% of women were qat chewers (64). In a recent survey from Sana'a and neighbourhood villages, it was found that 90% of men and 20% of women were regular qat chewers (30).

2.3. Women and qat use

According to the literature, women did not chew qat in the past. Moreover, no written accounts exist on when women started chewing it, but it could be assumed that the habit of qat chewing started to spread among women in the 1930s and 1940s. Al-Yahya, quoted in Sayem (31), visited Yemen in 1940, and he has stated that the ugliest habits among women were smoking, "hubble-bubble" (water-pipe) and chewing qat. Qat consumption has become more prevalent among women since the early 1960s and until recently, qat gatherings were restricted to rich families. In middle and lower classes, women rarely chewed (32). They also reported that qat gatherings are familiar among married and divorced women but never practiced among unmarried girls.

The main reasons for qat chewing among women were the need to cool off and the desire to rest after an exhausting day (33). Women consumed smaller quantities and chewed less long hours than men (34). Women now chew qat more than in the past and the chewing habit has become an integral part of their social and cultural life (2). A study among 200 students (100 males and 100 females) of Sana'a University found that 70 % and 10 % of males and females, respectively, chewed qat (35). A recent study among 805 women in Sana'a found that 77 % were chewers and among these only 46 % were daily chewers (31). The motives for chewing were to study, to socialize, for recreation, no alternatives, and to rest after an exhausting day (31). Qat chewing is no longer a male emblem as it was traditionally, but has entered the women's sphere (36). However, not in all areas do women chew qat, this habit seems to be still a shameful (*aib*) habit for women in some parts of the country (26).

2.4. The practice of qat chewing

In Yemen, chewing sessions are a very important part of the culture. Yemenis construct their houses to provide a warm reception to their qat-chewing guests. A special room specifically designed for the chewing called *mafraj* or *majles* (2) (figures 1, 2). These rooms are finely decorated and furnished with colourful comfortable mattresses,

cushions and arm rests for reclining and rest (26, 31). Qat chewing covers all social occasions such as weddings, births and other ceremonies (2, 26). Qat sessions always start in the afternoon between 2:00 and 8:00 pm, and in the gathering room each person is careful to choose a seat appropriate to his relative status. During chewing, windows and doors of the room kept tightly closed to create a dense atmosphere of smoke and heat. Each chewer makes himself comfortable by reclining against the firm back cushion, resting his left forearm on a moveable arm rest, his left leg is curled back on the seating cushion, the right is perpendicular to the floor, and he starts chewing in the left side of the mouth (Figures 3, 4). This might be due to the need of the chewer to free the right hand to use it when necessary in writing, explaining, etc. Few people may rest on their right forearms and subsequently chew in the same side of the mouth. Each chewer opens his plastic bag, picking some branches out, taking some tender leaves between his fingers, tucking into some side of the mouth and begins to chew. Chewing continues during conversation and other activities until the cheek grow into a noticeable ball, this process is called qat chewing (12) (figures 5, 6, 7, 8, 9).

2.5. Effects of qat chewing on social live in Yemen

Qat usually improve social relationship in the society. However, the family relationship as well as the relationship between parents and children may be affected negatively due to this habit (31, 32, 37, 38, 39, 40). The effects of qat chewing on the family budget have been studied (36, 39, 41). It was found that spending for qat accounted for between 9-20% of the family budget among middle class and reached 50% of the budget in the poor class. This may result in reducing the share of the income available for child nutrition and other basic needs and in some cases children are forced to work or deprived of education (36). Furthermore, the family budget deficit may result in seeking other illegal sources of income such as bribes and corruption (39).

2.6. Environmental effects of the growing of qat

Due to the high economic importance of qat as a cash crop, farmers tend to use pesticides and fertilizers heavily on qat trees in order to protect them from pests, to ensure healthy foliage and thus to increase the yield and income. (42). Most of the side effects of fertilizers result from the inadequate knowledge among farmers, in the choice of fertilizers, nutrients combination, rate, method and timing of application, irrigation and

water management (42, 43). Intensive agricultural production of qat with nitrogen-based fertilizers form nitrate, and with some microorganisms in the soil and water leads to the formation of nitrite, which causes methemoglobinemia (difficulties in blood oxygen transport system), and which reacts with secondary amines forming nitrosamines in food. Nitrosamines cause liver damage and hemorrhagic lung lesions in rats (44) and the N-nitroso compounds are suspected of playing causative role in various forms of cancer after a long latency period (45). Other environmental hazards come from the increased use of plastic bags, used by qat merchants to keep qat leaves fresh and to protect them from drying out. Polychlorinated biphenyls (PCBs) are known as being contaminants of soil and water (46).

2.7. Botany of qat

Catha Edulis is an evergreen tree with a straight and slender stem and white bark. The serrated leaves are elliptical in shape and are generally between 50-100 mm long and 30-50 mm wide (Figure 10). The plant has small petal white flowers of yellowish or greenish tone and range between 2-10 meters in height (Figures 11, 12, 13). Qat is a hardy plant, and it is drought-resistant and long-lived. The tree does not seem to suffer mineral deficiency as its deep root system can tap the minerals (2). Qat is an altitude crop that does not take much space and best cultivated at 1,500 – 2,400 m, and rare below 1200 above the sea level. The plant performs best where the average temperature is around 19 degrees centigrade (26, 47).

2.8. Chemistry of qat

Before analyzing the active ingredients of qat, early workers were of the opinion that qat's active ingredients were similar to those of coffee. When qat was analyzed in 1887, no caffeine was found, instead a new alkaloid was isolated and it was given the name cathine (48). This finding continued to be reported in literature for a long period (49, 50). Much later, in 1963, Friebel and Brilla (51) found another alkaloid - beside cathine - in a relatively high concentration; its structure, however, could not be determined. The new alkaloid was found to be more potent than pure cathine in stimulations the CNS of mice. Extensive studies of qat active constituents were done by many groups including United Nations Narcotics Laboratory (52, 53, 54, 55, 56).

They reported that the phenylalkylamine fraction of the qat alkaloids contained another compound in addition to cathine which was called cathinone later. The United Nation Narcotics Laboratory Reports no. 8 and 9 concluded that cathinone is a biosynthetic precursor that accumulates in young leaves while in adult leaves it undergoes enzymatic reduction to the less active compounds cathine and norephedrine. This finding supports the fact that qat users prefer the young leaves from the tips of the branches suggesting high concentration and stimulating effect of cathinone (55). The amount of alkaloids in 40 types of different fresh Yemeni qat was evaluated (57) and results showed that the concentration of the total cathinone and cathin ranged between 78 to 342 mg out of 100 grams of fresh qat obtained from each type. The amount of cathinone in four types of fresh qat was recently investigated (58). The amount found was 343 mg in Nihmi, 323 mg in Sawti, 127 mg in Dholah and 122 mg in Qatabi out of 100 mg of fresh leaves from each type.

Qat also contains a group of alkaloids called cathedulins, so far eleven alkaloids of this type have been isolated and characterized (58). Flavanoids are another important ingredient of qat exhibiting a high content of tannins. Tannins are a group of phenolic compounds and their concentrations vary depending on the type of qat (5). The concentration of tannins reported by Alles and co-workers ranges between 5.58% and 7.4% (5). Recently, Revri reported a concentration of tannins between 6-11% in five types of qat (47).

Variations in the tannin content of qat are primarily due to environmental differences rather than to differences between cultivars. Amount of tannins in qat leaves was shown to be affected by the amounts of calcium in the leaves, amounts of nitrogen in soil and the altitude, i. e. the higher the percentage of calcium the lower the tannins' content. At the same time the higher the nitrogen content in the soil, the higher the tannins' content. Qat also contains a significant percentage of vitamin C (5, 6). In addition to that 17 types of amino acids were isolated from fresh qat leaves.

2.9. Pharmacology of qat

Cathinone which is the main constituent of qat is rapidly absorbed after oral administration compared to cathine, which is absorbed slowly (9). Cathinone is highly lipid soluble; this characteristic facilitates its access into the central nervous system (9). The maximum effects of cathinone were found after 15-30 minutes from its oral

administration (59). Cathinone is metabolized in the liver into norephedrine and is excreted almost exclusively in this form; only about 2% of cathinone absorbed appears unchanged in the urine (60). The rapid rate of inactivation of cathinone is almost the same as the rate of absorption during chewing. That is why the level of cathinone in the blood is limited during qat chewing (9). The sympathomimetic effects of qat are due to the concurrent action of cathinone and of cathine, whereas its central nervous system effects are almost entirely due to cathinone. Indeed, cathinone is more potent than cathine with regard to central nervous stimulation and more lipophilic than cathine (9). Cathinone is a potent amphetamine-like substance, which shares the pharmacological profile and features of amphetamine with regard to their central nervous system effects (61, 62). It is important to recall that amphetamine is an indirectly acting adrenergic drug; it causes the release of catecholamines in the central nervous system and prolongs their action (63). Actually, only very few differences between cathinone and amphetamine are found. The development of tolerance with cathinone is much more unlikely pronounced in comparison with amphetamine (64). The central nervous system effects of qat usually do not develop any tolerance (8), except for cases of insomnia (65) and anorexia (66).

A WHO expert group on drug dependence (67) has extensively revised the previously reported dependence induced by cathinone. They concluded that cathinone induced neither physical dependence nor addiction (65, 67, and 68).

2.10. Systemic effects of qat

2.10.1. Effects of qat on CNS

The popularity of qat chewing is mainly due to its major active ingredient cathinone (9). Its effects in the human body appear within a period of 2-4 hours on average of qat chewing (11). Qat provides psycho-stimulant effects in the form of moderate euphoria and mild excitement (7, 69). Also it increases the alertness and energy and produces an enhanced depth of perception (70, 71); these psycho-stimulant effects are progressively replaced in many chewers by mild dysphoria, anxiety, reactive depression, insomnia and anorexia (72, 73). Sometimes chewers try to overcome insomnia with sedatives or alcohol (7, 8). The simultaneous and excessive effects of smoking may also influence the symptoms produced by qat chewing (7, 8).

2.10.2. Effects of qat on cardiovascular system

The sympathomimetic effect of cathinone and cathine leads to a significant rise of arterial systolic and diastolic blood pressure and pulse rate (73, 74). The peak effect on the arterial blood pressure and pulse rate is reached 3 hours after starting to chew, followed by a decline 1 hour after spitting the leaves out. These changes run parallel with changes in plasma cathinone levels during and after qat chewing (75). The cathinone responsibility for the increase in arterial blood pressure and pulse rate during qat chewing is supported by Brenneisen et al. who observed a similar blood pressure increase in subjects who have taken a pure cathinone in gelatine capsules orally (60, 76). A study conducted by Hassan et al. revealed that the increase of blood pressure is due to the stimulant effect of cathinone on beta-one adrenoceptor in the heart (77). Qat chewing may be a potential cardiovascular risk factor in patients with hypertension and heart diseases, and may precipitate the occurrence of cerebrovascular accidents and myocardial infarction in susceptible individuals (78). The aforementioned is supported by AL-Motarreb who carried out a study on guinea pigs. He found that cathinone can induce vasoconstriction of the coronary vascular bed (79).

2.10.3. Effects of qat on digestive system

Clinical observation found that qat chewers often complain of symptoms suggestive of oesophagitis and gastritis. The strongly astringent tannins in qat were blamed as a causative substance of the digestive disorders (13, 80). Other studies concluded that the sympathomimetic action of cathinone did indeed delay gastric emptying of a semi-solid meal (72, 80). Anorexia was noted after qat chewing (72) and this significant reduction of appetite after qat chewing may be attributed to combined direct central and gastric effects of cathinone (72). Common complaint among qat chewers is constipation, which is probably due the astringent properties of the qat tannins (9). Habitual users try to attenuate this undesirable effect by laxatives or by eating a meal with high fat content prior to the qat session in order to facilitate intestinal transit (8). Additionally reports state that chewing qat leaves significantly slows both the oro-caecal transit time (81) and the whole gut transit time (82). The liver has been suspected to be particularly vulnerable to the harmful effects of qat use (8, 65) and a disturbance in liver function and architecture has been described in experimental animals both on short-term (83) and long-term studies (84).

2.10.4. Effects of qat on genitourinary system

One of the obvious side-effects of chewing qat leaves in males is temporary difficult micturition with hesitancy and poor flow. Overall urine flow rates were recently found to be significantly lower in qat users (85). This effect is probably mediated through stimulation of beta-one adrenoceptors in the bladder neck by the sympathomimetic effects of cathinone. These effects were abolished by the beta-one adrenoceptor blocker indoramin. The consumption of qat is found to induce an increase in libido, spermatorrhoea and erectile dysfunction (70).

2.10.5. Effects of qat on the health of pregnant women and foetus

In the domain of reproductive health, epidemiological data derived from 1181 deliveries in Yemen showed that at birth the mean weight of full-term singleton infants from mothers who chewed qat habitually or occasionally was below average (86). A study on pregnancy outcome and qat showed a significantly increased incidence of low-birth-weight full-term infants among the offspring of women who chewed qat during pregnancy in comparison to those who were non-chewers during pregnancy (87). Recent evidence has indicated that neonates of mothers who chewed qat during pregnancy had a significant decrease in all neonatal parameters such as birth weight, length, and head circumference in comparison with those of mothers who did not chew qat during pregnancy (88). This effect was found to increase in severity with the increased frequency and duration of qat chewing during pregnancy. An experimental study in rats has recently proved that qat can affect intrauterine fetal growth by reducing total fetal fat and weight and by inducing some changes in the chemical composition of fetal organs, particularly the liver, heart and kidneys (89). The author attributed that effect to depletion of carbohydrate material and suppression of DNA and protein synthesis in the fetal organs. Nursing mothers in Yemen frequently complain of poor lactation. Some authors believe that this phenomenon may be related to the use of qat as cathine in qat may inhibit prolactin secretion (65). Interestingly, it has been found that the breast milk of qat-chewing mothers contains cathine, and this compound could even be detected in the urine of one breastfed infant (90).

2.11. Effect of qat chewing on oral tissue

2.11.1. Effects of qat chewing on periodontal tissues

Earlier studies on periodontal condition among different ethnic groups in Israel found a high rate of periodontal disease among Yemeni emigrants due to qat chewing (91). Long term qat chewing was reported to cause stomatitis followed by secondary infection which might be related to mechanical trauma and chemical content of qat (8). A high rate of periodontal disease has been observed among Yemeni male qat chewers (65). On the other hand, significantly deeper periodontal pockets were reported on the opposite side of chewing compared to chewing sites and were claimed to have beneficial effects of qat chewing on periodontal tissues (14). Moreover, in Kenya, no significant differences were found in periodontal health among 131 mirra (mirra is the name of qat in Kenya) chewers and 199 non mirra chewers. Additionally, significantly lower lingual plaque and gingivitis scores among mirra chewers than non mirra chewers were reported (92). The authors concluded that no evidence was found indicating that chewing is detrimental to periodontal health. The community periodontal index of treatment needs, clinical attachment loss and calculus index were higher among 1001 Yemeni qat chewers than non chewers. Differences were significant for the 12-24 years age group while insignificant for those in the 35-44 years age group (93). The same study also showed that scores of attachment loss were lower among chewers than scores among non chewers. Recently, a cross sectional hospital study among Yemeni qat chewers and non chewers revealed an increased risk for a number of periodontal lesions (12). The study revealed that qat chewing causes many lesions to the supporting structure of the teeth, namely gingivitis, periodontal pocket formation, gingival recession, tooth mobility and finally tooth mortality.

2.11.2. Effects of qat chewing on hard tissues of the teeth

Effects of qat chewing habit on the hard tissues of teeth have been reported by many researchers. The earliest investigation reported that a low rate of dental caries was observed among Yemeni qat chewers (65). Discolored and missing teeth were reported among Yemeni qat chewers (8). Low caries rate and universal attrition was reported among 115 qat chewers examined. The prevalence of dental caries was less than 2% of all teeth examined. The low prevalence of dental caries among qat chewers was attributed either to the high contents of fluoride in water or to the amount of fluoride

available in qat leaves (14). A recent investigation found no association between conventional (occlusal) dental caries scores and qat chewing among 325 Yemeni qat chewers (12). The same study reported a strong association between qat damaging effects to dental tissues in the forms of attrition, staining and cervical caries. Attrition and staining were found among 52.6% and 82.8% of 325 qat chewers, respectively. Cervical caries was found among all chewers consuming crystallized sugar during chewing (12). Certain types of qat are bitter in taste, therefore many chewers use sweet drinks or crystallized sugar to compensate the taste during chewing (2, 12, 65).

2.11.3. Effects of qat chewing on temporo-mandibular-joint (TMJ) and facial tissues

The effects of qat chewing on TMJ pain, clicking and facial asymmetry had been investigated. Early reports found TMJ-related pain among 40% of 115 qat chewers examined (14). TMJ related clicking and pain and facial asymmetry among qat chewers were studied extensively (12). TMJ-related clicking was found among 109 subjects, of them 27 (24.8%) suffered from pain. Clicking was attributed to the overloading of the condyle surface due to chewing forces. Obvious facial asymmetry was present among 75.4% of the qat chewers examined which was correlated positively with long duration of the qat chewing habit (12). This could be attributed to muscle hypertrophy due functional demand.

2.11.4. Effects of qat chewing on salivary glands

The effects of qat chewing on the dryness of the mouth among chewers have been documented in many reports (2, 9, 94). The authors substantiated that the aetiology of xerostomia might be due to the sympathomimetic effects of cathinone or due to the over-excretion of saliva from salivary glands during chewing. The effects of qat chewing on saliva and salivary glands were extensively studied (12). The results showed strong causal relationship between qat chewing and xerostomia, enlargements of major salivary glands and inflammation and enlargements of parotid duct opening. No clear effects of qat chewing on salivary viscosity was found, however, there was an obvious effect on salivary flow after qat chewing, as 67.4% complained of xerostomia for many hours after qat chewing. The enlargement of major salivary gland might be due to over-exhaustion of continuous over-secretion for many hours per day for decades. The

inflammation found on parotid opening at the site of chewing was probably due to long-term friction of qat fibres. The folded papilla might be a defence mechanism to prevent qat particles from entering the duct in similar mechanisms observed in pipers (12).

2.12.1. Histopathological studies

Before histopathological studies were performed of the oral mucosa, information was obtained from histopathological studies of the upper gastrointestinal tract among qat chewers. In this study, regular daily qat chewing was not associated with a significant effect on the esophagus (95). Additionally, mild abnormal growth of gastric mucosal cells (dysplasia) and abnormal intestinal cells (metaplasia) at the lower esophagus were higher in qat chewers than non chewers (96). Buccal and gingival mucosa at sites of qat chewing among Yemeni chewers had been extensively studied histopathologically in the past 6 years (12, 97, 98). The earliest investigation was done on 42 biopsies divided into 3 groups. Group 1 included 30 biopsies from sites of chewing (13 were chewers and cigarette smokers and 17 were chewers and non-smokers). Group 2 included 7 biopsies taken from the non-chewing sites of qat chewers (5 were chewers and smokers and 2 were chewers and non-smokers). The results revealed that histopathological changes found on oral mucosa included increased rete ridges, acanthosis, intercellular edema, orthokeratosis, parakeratosis, epithelial dysplasia, inflammatory cell infiltrate and increased amount of collagen fibers (12). All results were statistically significant except for results of epithelial dysplasia and inflammatory cell infiltrates. Also the distribution of histopathological cases among smokers and non smokers were statistically not significant (12). Another investigation was done on 40 biopsies divided equally into two groups taken from gingival and buccal mucosa of chewing and opposite sides (97). Results showed apparent histopathological differences between the 2 groups and all alterations were similar to those reported earlier (12). An investigation was done recently to further study different histopathological effects on oral mucosa among qat chewers due to qat chewing (98). Results similar to previous those of studies were reported. The authors concluded that qat chewing caused innocuous histopathological changes at site of chewing without any malignancy (97, 98).

2.12.2. Effects of qat chewing on oral mucosa and oral cancer

Effects of qat chewing on oral mucosa and oral tumours have been investigated by many authors. Tumours of the oral cavity (including lower maxilla, buccal mucosa and lateral border of the tongue) were reported in n=74 (0.13%) out of 5757 patients seeking treatment in a stomatology clinic in Hodeidah, Yemen, over a two years period (17). The majority of cases were men over 40 years of age who had chewed qat and or used shammah (snuff) for 20 years or more. No oral cancer has been reported from comprehensive evaluation of 706 Yemeni qat chewers (335 female and 371 male) in the age range 15-60 years (13). Mucosal changes or some degrees of oral keratosis were found at the site of chewing among 50% of qat chewers. However, no cancerous lesion was diagnosed (14). Occurrence of oral cancer in a study conducted over a two year period in Asir region was reported (18). Out of 28 head and neck cancers, 10 cases (7 males and 3 females, age ranged 25-40 years) were diagnosed in the mouth mostly in the anterior two thirds of the tongue and floor of the mouth. No information of shammah use was provided despite fact that the inhabitants in the area of the study are known to be shammah dippers. One case of oral verrucous carcinoma with a history of tobacco chewing, snuff dipping and qat chewing was reported (19). In Kenya, the association between leukoplakia, smoking, alcohol consumption and qat chewing has been studied (15). Results showed that qat chewing was not significantly associated with leukoplakia. 17 cases of head and neck carcinoma were diagnosed during a one year period among chronic qat chewers (99). Of these cases, 10 were also snuff dippers and 5 others were smokers. In a cross sectional hospital-based study, 431 subjects (325 chewers and 106 non chewers) were recruited. All those 325 subjects who chewed qat for not less than 3 years demonstrated buccal and gingival white lesions. 100% and 90% of mucosal changes were on buccal and gingival mucosa, respectively (12), no dysplasia or cancer was reported. Another study reported 342 mild keratotic white lesions among Yemeni qat chewers (16). Oral white lesions were reported among 47 Yemeni Israeli Jews above the age of 30 years with duration of qat chewing of more than 3 years. According to this study, white lesions due to qat chewing were seen at the site of chewing with no atypical epithelial cells observed. No suggestive premalignant or malignant changes were identified in the subset of patients (100).

Recently, a study done in vitro to see the effects of qat extracts on oral keratinocytes and fibroblasts showed that qat extracts inhibited the proliferation of oral keratinocytes

and increased expression of stress-sensitive p53 protein and p16 protein after 24 hours. On fibroblast qat extracts also inhibited the proliferation and increased expression of p21 protein after 24 hours (101).

There is not enough evidence in the literature that qat chewing alone is carcinogenic or that it plays an independent direct role in the development of head and neck cancers. Unfortunately, the frequent combined use of qat and tobacco products makes it difficult to isolate the contribution each makes to the risk of developing oral cancer. Although the exact mechanism of any reported carcinogenesis is unknown, available information suggests that qat chewing should be considered one of the possible confounding risk factors for oral cancer specific to individuals who practise qat chewing along with tobacco use (102).

3. MATERIAL AND METHODS

3.1. Materials

The aim of this study was to use quantitative epidemiological methods to assess and document the clinical characteristics for oral white lesions among Yemeni female qat chewers. So far, these lesions were observed mainly among male chewers and were hypothesized to be induced by qat chewing.

The design of the study was hospital-based cross sectional. Qat chewing was the exposure and the white lesions produced considered the outcome or the disease status. The epidemiological approach was a retrospective cohort, as the exposure was well ascertained because the qat chewing habit is widespread and socially accepted. Therefore, the analysis was performed from the exposure to the disease status. The exposure was ascertained simultaneously with the disease status. The analysis therefore emphasized the exposure and then the outcome, the disease status. It was then found appropriate to consider a retrospective cohort analysis.

Subjects of this study were female patients who presented to dental clinics of Al-Thawra health institution in Sana'a city for dental treatment during the period 2006-2008. Sana'a is the capital of Yemen which has a population of more than 2 million representing most ethnic and social strata of Yemenis.

Participation of subjects in the study was according to the following criteria:

Criteria of selection:

- Adult Yemeni healthy qat chewing females aged 20-65 years.
- Continuous qat chewers for at least 5 years.
- Chewers on one side of their mouths only.

Exclusion criteria:

- Bilateral chewers (chewers in both sides of their mouths).
- Shammah users.
- Poor general or mental health.

Participants were subjected to a detailed clinical examination of oral mucosal tissues at chewing sites and opposite sides:

- The chewing sites among female qat chewers were dealt with as cases of the study.
- The contralateral side of female qat chewers were dealt with as control 1.
- Both sides of female non-qat chewers were dealt with as control 2.

3.2. Methods

Procedure of investigation:

The procedure of the investigation started as patients arrived at the dental clinic of the Althawra Health Institute. In the dental clinic, female patients reported their histories and main complaints. Before examining the patients, the investigator (JS) introduced himself and briefly talked with each female patient to obtain her consent and also to assess her suitability to be selected for the study. If the female patient was found to be an eligible candidate according to the inclusion criteria, the study commenced using the short interview questionnaire and the clinical examination sheet (appendix).

Materials of interview:

The interview questionnaire included following information:

- Personal data (name, age, residence and address).
- Information on qat (frequency of habit / week, intraoral site of chewing, age of starting chewing, duration of the habit /years, average period of each session /hours).
- Information on cigarettes (cigarettes smoking situation, duration of smoking / years and frequency of smoking /day).
- Information on water-pipe (water-pipe smoking situation, duration of water-pipe smoking / years and frequency of water–pipe smoking /day).
- Oral hygiene status (OHS) (use of tooth brush or other oral hygiene aids, frequency of tooth brushing).

3.3. Clinical examination

Participants were subjected to a detailed clinical oral examination including oral hygiene status and oral mucosa at the site of chewing and at the opposite side.

Oral hygiene status examination included the state of oral hygiene, whether it was good, fair or poor by assessing the amount of dental plaque collected on teeth. Each participant was asked if she was a toothbrush user or not, if yes, what type of device she used for mouth cleaning and how many times a day.

Examination of the oral mucosa started by inspecting buccal mucosa on the internal surface of the cheek, inspecting buccal mucosa and its continuation or extensions up to the upper vestibular mucosa and down to lower buccal and lower vestibular mucosa. Buccal mucosa was reflected sufficiently and inspected carefully for any mucosal changes in colour and texture on both sides of the mouth.

Gingival mucosa and its extension to alveolar mucosa were also inspected carefully for any mucosal changes in colour and texture on both sides of the mouth.

White lesion (leukoplakia) was defined as lesion at the site of qat use that could not be removed and was not clinically suspected as any other white lesion. It was scaled using the previous scale of white lesions due to qat chewing (16).

Inspection also included the presence of any other mucosal changes or lesions such as leukoedema, frictional keratosis at the site of chewing and the opposite side.

Careful bimanual palpation of all mucosal surfaces was performed to examine the underlying structure and to find out if the patient felt any pain. Clinical examination was carried out using two disposable dental mirrors with the patient lying on a dental chair using artificial light.

Ethical considerations:

Aim of the study was explained to each subject and only patients who consented voluntarily to participate were included in this study. Following the clinical examination all patients were treated free of charge.

3.4. Statistical analysis

Data from the questionnaires and case sheets were processed using a statistical software package (SPSS version 15). The level of significance was set at $p < 0.05$. Univariate comparisons between patient and controls were made for the potential risk factors using the chi square test and OR and their 95 % CI for the nominal and categorical variables.

A multinomial logistic regression model was used to identify the significant association of the difference potential risk factors as independent variables with the presence of white lesion as the dependent variable.

4. RESULTS

4.1. Age and qat chewing habit

The total number of subjects recruited in this study according to the previous criteria was 162. All of them were medically healthy Yemeni females, divided into 109 qat chewers and 53 non-chewers.

Table 1 shows distribution of age and habit of chewing

The mean age was 38.25 years; ranging from 20 to 65 years. No significant difference was found between chewers and non-chewers in terms of age distribution.

Table 1: Distribution of the patients according to age and qat chewing habit

Age Group(years)	Chewers		Non-chewers		Total	
	Count	%	Count	%	Count	%
20 - 29	26	23.9	15	28.3	41	25.3
30 - 39	39	35.8	11	20.8	50	30.9
40 - 49	27	24.8	10	18.9	37	22.8
50 - 59	11	10.1	12	22.6	23	14.2
60 - 69	6	5.5	5	9.4	11	6.8
Total	109	100	53	100	162	100

4.2. Residence

Residence distributed by town vs. village among the study population is shown in table 2. The majority of the study population lived in towns (n=110 / 67.9%) compared to 52 (32.1%) living in villages. Thus, 76 (69.7%) chewers lived in towns and 33 (30.3%) in villages. Similarly, 34 (64.2%) non-chewers lived in towns and 19 (35.8%) subjects in villages.

Table 2: Distribution of residence town/village

Residence	Chewers		Non-chewers		Total	
	Count	Col %	Count	Col %	Count	Col %
Town	76	69.7	34	64.2	110	67.9
Village	33	30.3	19	35.8	52	32.1
Total	109	100	53	100	162	100

No significant difference was found between subjects living towns and those living in villages in terms of their chewing habits ($p= 0.476$).

4.3. State of oral hygiene

Table 3 displays the state of oral hygiene (OHS) among the study population.

Among chewers, the distribution of oral hygiene status was as follows:

22 (20.2%) had good OHS, 21 (19.3%) had fair OHS, 66 (60.6%) had poor OHS.

Among non-chewers, 24 (45.3%) had good OHS, 15 (28.3%) had fair OHS, and 14 (26.4%) poor OHS. Non-chewers, however, had better OHS than qat chewers and the difference was statistically significant ($p=0.000$).

Table 3: State of oral hygiene

State of oral Hygiene	Chewers		Non-chewers		Total	
	Count	%	Count	%	Count	%
Good	22	20.2	24	45.3	46	28.4
Fair	21	19.3	15	28.3	36	22.2
Poor	66	60.6	14	26.4	80	49.4
Total	109	100	53	100	162	100

4.4. Tooth brushing behaviour, type of brush and brushing frequency

Use of tooth brushing tools among the study population showed that 105 (64.8%) brushed their teeth, and the remaining 57 (35.2%) did not brush their teeth. Of chewers, 64 (58.7%) were toothbrush users and the remaining 45 (41.3%) were non-users. Of the non-chewers, 41 (77.4%) were toothbrush users and the remaining 12 (22.6) were non-users (table 4).

Type of brush used for mouth cleaning among study populations was distributed as follows: 17 (16.2%) were miswak users (miskwak is a traditional tooth brush used in Arabia and India), and 77 (73.3%) were toothbrush and paste users. Of the latter group, 11 (10.5%) used dental floss and other oral hygiene aids. Among chewers, 11 (17.2%) were miswak users, 49 (76.6%) toothbrush and paste users, the latter group 4 (6.3%)

used dental floss and other tooth cleaning aids. Among non-chewers, 6 (14.6%), 28 (68.3%), 7 (17.1%) were miswak users; toothbrush and paste users and dental floss users respectively (table 4).

Frequency of brushing per day among the study population was distributed as follows: 40 (38.1%) brushed once, 60 (57%) brushed twice, 5 (4.8%) brushed their teeth more than twice a day. Among chewers, 25 (39.1%) brushed once, 35 (54.7%) brushed twice, and 4 (6.3%) brushed more than twice a day. Of the non-chewers, 15 (36.6%) brushed once, 25 (61.0%) brushed twice, and 1 (2.4%) brushed more than twice per day (table 4).

Table 4: Description of tooth brushing behavior, type of brush and brushing frequency

Description	Chewers		Non-chewers		Total	
	Count	Col%	Count	Col %	Count	Col %
Tooth brushing						
users	64	58.7	41	77.4	105	64.8
Non-users	45	41.3	12	22.6	57	35.2
Total	109	100.0	35	100.0	162	100.0
Type of brushing and oral health aids						
Miswak	11	17.2	6	14.6	17	16.2
Toothbrush and paste	49	76.6	28	68.3	77	73.3
Dental floss& other aids	4	6.3	7	17.1	11	10.5
Total	64	100.0	41	100.0	105	100.0
Frequency brushing per day						
Once	25	39.1	15	36.6	40	38.1
Twice	35	54.7	25	61.0	60	57.1
More than two	4	6.3	1	2.4	5	4.8
Total	64	100.0	41	100.0	105	100.0

4.5. Age of starting chewing and predominant side of chewing

Table 5 shows the distribution of chewers according to their age of starting qat chewing. The distribution was as follows:-

34 (31.2%) started chewing at 10-20 years of age,
 52 (47.7%) started chewing at 20-30 years of age
 23 (21.1%) started chewing at 30-40 years of age

Table 5 also shows the intraoral side which was mainly used to chew.

The distribution was as follow:

16 (14.7%) chewers chew on their right side
 93 (85.3%) chewers chew on their left side.

Table 5: Distribution of chewers according to their age of starting chewing and predominant mouth side of chewing

Distribution	Count	%
Age of starting qat chewing (years)		
10 - 20	34	31.2
20 - 30	52	47.7
30 - 40	23	21.1
Total	109	100
Oral side of chewing		
Right	16	14.7
Left	93	85.3
Total	109	100

4.6. Duration of qat chewing habit / year/, frequency/week and sessions/hours (Table 6)

Duration of qat chewing among chewers ranged from 5 to 40 with a mean of 14.79 years.

Duration of qat chewing among chewers was as follows:

57 (52.3%) had chewed for (5-14) years, 39 (35.8%) had chewed for (15-29) years, and 13 (11.9%) had chewed for (30-44) years.

Frequency of chewing habit / week:

The frequency of qat chewing habit among study cases per week were as follows:

32 (29.4%) used to chew only (1-2) days per week, 10 (9.2%) chewed for (3-5) days / week, and 67 (61.5%) chewed for (6-7) days / week.

Average period of qat session /hours:

The average periods of each qat chewing session / hours were as follows:

29 (26.6%) chewed qat on average for (1-2) hours / day, 55 (50.5%) chewed qat on average for (3-5) hours / day, 25 (22.9%) chewed qat on average for (>6) hours / day.

Table 6: Distribution of qat chewers according to duration/years, frequency of habit per week, average time/hours

Distribution	Count	%
Duration of the habit in years		
5 - 14	57	52.3
15 - 29	39	35.8
30 - 44	13	11.9
Total	109	100
Frequency of the per week		
1 – 2	32	29.4
3 – 5	10	9.2
6 – 7	67	61.5
Total	109	100
Period of each session in hours		
1 – 2	29	26.6
3 – 5	55	50.5
> 6	25	22.9
Total	109	100

4.7. Cigarette smoking, duration /years and frequency / day

Table 7 shows the distribution of cigarette smoking, duration of smoking/year and frequency of smoking/day.

Among chewers, 21 (19.3%) were smokers, 88 (80.7%) were non-smokers.

In the non-chewers group, only 9 (17.0%) were smokers, the remaining 44 (83.0%) were non-smokers.

The duration of smoking in years was as follow: Among chewers, 8 (38.1%) had smoked for less than 10 years, 8 (38.1%) had smoked for 10-19 years and 5 (23.8) had smoked for more than 20 years.

Among non-chewers, 4 (44.4%) had smoked for less than 10 years, 4 (44.4%) for 10-19 years and 1 (11.1%) for more than 20 years.

The number of cigarettes per day was as follows: Among chewers, 9 (42.9%) had smoked less than 10 cigarettes per day, 8 (38.1%) less than 20 cigarettes and 4 (19.0%) more than 20 cigarettes per day. Non-chewers were 7 (77.8%) who had smoked less than 10 cigarettes per day and 2 (22.2%) more than 10 and less than 20 cigarettes per day.

Table 7: Distribution of cigarette smoking, duration/year and number of cigarettes/day

Description	Chewers		Non-chewers		Total	
	Count	%	Count	%	Count	%
Smoking habit.						
Smokers	21	19.3	9	17.0	30	18.5
Non-smokers	88	80.7	44	83.0	132	81.5
Total	109	100	53	100	162	100
Duration of smoking in years.						
< 10 years	8	38.1	4	44.4	12	40.0
10 – 19 years	8	38.1	4	44.4	12	40.0
> 20 years	5	23.8	1	11.1	6	20.0
Total	21	100	9	100	30	100
Number of cigarette per day.						
< 10 cigarette daily	9	42.9	7	77.8	16	53.8
10-20 cigarettes daily	8	38.1	2	22.2	10	33.3
>20 cigarette daily	4	19.0	--	--	4	13.3
Total	21	100	9	100	30	100

4.8. Water-pipe smoking duration/year and frequency/day

Tables 8 show the distribution of water-pipe smoking, duration / years and frequency / day.

The distribution was as follows: Among chewers, 13 (11.9%) were water-pipe smokers, 30 (27.5%) were water-pipe smokers with qat and the remaining 66 (60.6%) were non-users. In the non-chewers group, only 9 (17.0%) were water-pipe smokers, 44 (83.0%) did not use the water-pipe. This difference was significant ($p=0.004$).

The duration of the water-pipe smoking habit showed that among chewers, 14 (32.6%) had smoked for less than 10 years, 10 (23.3%) for 10-19 years and the remaining 19 (44.2%) had smoked for more than 20 years.

The frequency of water-pipe smoking per day showed that 22 (51.2%) had smoked only once a day, 13 (30.2%) had smoked twice and the remaining 8 (18.6%) had smoked more than two times per day.

Among non-chewers were 6 (66.7%) who had smoked only once a day and 3 (33.3%) twice a day.

Table 8: Distribution of water-pipe smoking, duration/years and frequency/day

Description	Chewers		Non-chewers		Total	
	Count	%	Count	%	Count	%
Water-pipe Smokers						
Users	13	11.9	9	17.0	22	13.6
Non-users	66	60.6	44	83.0	110	67.9
With Qat only	30	27.5	--	--	30	18.5
Total	109	100	53	100	162	100
Duration of water-pipe smoking						
< 10 years	14	32.6	4	44.4	18	34.6
10 – 19 years	10	23.3	4	44.4	14	26.9
> 20 years	19	44.2	1	11.1	20	38.5
Total	43	100	9	100	52	100
Frequency per day						
Once	22	51.2	6	66.7	28	53.8
Twice	13	30.2	3	33.3	16	30.8
More than two	8	18.6	--	--	8	15.4
Total	43	100	9	100	52	100

4.9. White lesion

White lesions in this study occurred on buccal mucosa as mild keratotic white lesion with no leukedema or leukoplakia (figures 14, 15).

4.9.1. White lesion detected among the whole study subjects (table 9)

White lesions in this study were detected among 89 (54.9%) subjects. The extension from buccal mucosa to lower buccal mucosa were detected in 58 (65.1%), to lower

vestibular mucosa in 36 (62.1%), and to upper vestibular mucosa in 3 (5.1%) of the sides.

On gingival mucosa, white lesion were detected in 31 (34.8%), and extension to alveolar mucosa was found in 18 (58.1%) of the sides (table 9).

Table 9: distribution of white lesions among study subjects

Distribution of white lesion among study subjects	present		absent		Total
	count	%	count	%	
Normal	73	45.1	89	54.9	162
White lesion	89	54.9	73	45.1	162
Lower buccal mucosa	58	65.2	31	34.8	89
Lower vestibular sulcus	36	62.1	22	37.9	58
Upper vestibular sulcus	3	5.1	55	94.8	58
Gingival mucosa	31	34.8	58	65.2	89
Alveolar mucosa	18	58.1	13	41.9	31

4.9.2. White lesions detected among cases (table 10)

White lesions were detected in 82 (75.2%) of the cases, the extension from buccal mucosa to lower buccal mucosa was detected in 54 (65.8%) subjects. The extension to lower vestibular mucosa was detected in 36 (66.6%), and to upper vestibular mucosa in 3 (5.5%) of the chewing sites. On gingival mucosa white lesions were detected in 28 (34.2%). The extension to alveolar mucosa found in 15 (53.5%) (Table 10).

Table 10: Distribution of white lesions among cases (chewing site)

Distribution of white lesion on oral side of chewing among chewers	present		absent		Total
	count	%	count	%	
Normal	27	24.7	82	75.3	109
White lesion	82	75.2	27	24.7	109
Lower buccal mucosa	54	65.8	28	34.2	82
Lower vestibular sulcus	36	66.6	18	33.4	54
Upper vestibular sulcus	3	5.5	51	94.5	54
Gingival mucosa	28	34.2	54	65.8	82
Alveolar mucosa	15	53.5	13	46.5	28

4.9.3. White lesions detected among control 1 (table 11)

White lesion among control 1 were detected in 6 (5.5%) subjects. The extension from buccal mucosa to lower buccal mucosa was detected in 3 (50.0%), to lower vestibular mucosa detected in 1 (33.4%), and to upper vestibular mucosa detected in 1 (33.4%) of the opposite side. On gingival mucosa, white lesions were detected in 3 (50.0%) subjects.

Table 11: Distribution of white lesion on the opposite side among chewers (Control 1)

Distribution of white lesion on the opposite side among chewers	present		absent		Total
	count	%	count	%	
Normal	103	94.4	6	5.5	109
White lesion	6	5.5	103	94.4	109
Lower buccal mucosa	3	50.0	3	50.0	6
Lower vestibular sulcus	1	33.4	2	66.4	3
Upper vestibular sulcus	1	33.4	2	66.4	3
Gingival mucosa	3	50.0	3	50.0	6
Alveolar mucosa	0	0	3	100	3

4.9.4. White lesion detected among control 2 (table 12)

White lesions among control 2 were detected in 7 (13.2%) subjects. The extension from buccal mucosa to lower buccal mucosa was detected in 4 (57.2%), and to lower vestibular mucosa in 2 (50.5%) of the sides.

On gingival mucosa, white lesions were detected in 3 (42.8%) subjects. The extension to alveolar mucosa was found in 2 (66.6%) subjects.

Table 12: Distribution of white lesion among control 2 (Non-chewers)

Distribution of white lesion among non-chewers control 2	present		absent		Total
	count	%	count	%	
Normal	46	86.7	7	13.2	53
White lesion	7	13.2	46	86.7	53
Lower buccal mucosa	4	57.2	3	42.8	7
Lower vestibular sulcus	2	50.0	2	50.0	4
Upper vestibular sulcus	0	0	4	100	4
Gingival mucosa	3	42.8	4	57.2	7
Alveolar mucosa	2	66.6	1	33.4	3

4.9.5. Distribution of white lesions among study subjects and control 1 and control 2 (table 13)

White lesions were present in 82 (75.2%) at chewing site (subjects), in 6 (5.5%) on the opposite side (control 1) and in 7 (13.2%) among non-chewers (control 2).

Table 13: Distribution of white lesions among study subjects and controls 1 and 2

White lesions among study subjects	present		absent		Total	
	count	%	count	%	count	%
Chewers (cases)	82	75.2	27	24.8	109	67.3
Opposite side (control 1)	6	5.5	103	94.4	109	67.3
Non-chewers (control 2)	7	13.2	46	86.7	53	32.7
Total	89	54.9	73	45.1	162	100

4.10. Statistical evaluation

4.10.1. Correlations:

Residence

The residence (town, village) was examined for correlation with white lesions. Findings showed that white lesions found among women living in towns were higher than in women living in villages. The difference was highly significant ($p=0.000$).

State of oral hygiene and presence of white lesions

The state of oral hygiene was examined for correlation with white lesions. White lesions were predominant in women with bad oral hygiene ($p=0.000$)

Tooth brushing behaviour and presence of white lesions

Tooth brushing behaviour was examined for correlation with white lesions. Findings were significantly associated with not users of tooth brush ($p=0.000$) but also with tooth brush users ($p=0.000$). No significant difference was found between white lesion and type of brushing ($p=0.823$). Also frequency of brushing per day was examined for correlation with white lesions. Findings were significantly associated with tooth brushing once, twice and brushing more than twice a day ($p=0.048$).

Age of starting chewing and presence of white lesions

Age of starting of chewing was examined for correlation with white lesion. Findings were not significant ($p=0.339$).

Site of chewing and presence of white lesions

White lesions were significantly more frequent at the chewing site ($p<0.000$).

Duration of qat chewing habit (years), frequency (weeks) sessions (hours) and presence of white lesions

Duration of qat chewing was examined for correlation with white lesions. White lesions were significantly more frequent the longer the habit persisted ($p=0.000$) (figure 16).

White lesions were significantly more frequent the longer qat was used per week ($p=0.031$) (figure 17).

Average periods of each session in hours were examined for correlation with white lesions. Findings were highly significant ($p=0.000$) (figure 18).

Duration of cigarette smoking (years), frequency (day) and presence of white lesions

There was a positive correlation between cigarette smoking and white lesions ($p=0.026$).

Duration of smoking (in years) was not significantly correlated with the presence of white lesions ($p=0.742$).

No significant difference was found between frequency of cigarette smoking (day) and presence of white lesion ($p=0.267$)

Duration of water-pipe smoking (years), frequency (day) and presence of white lesions

Water-pipe smoking was positively associated with white lesions ($p=0.000$).

Duration of water-pipe smoking (in years) was not significantly correlated with the presence of white lesions ($p=0.084$).

Frequency of water-pipe smoking per day was examined for correlation with white lesions. Findings were not statistically significant ($p=0.311$).

Analysis of white lesions among study group (chewers) and group 2 (non-chewers)

Differences between white lesions (buccal and gingival) between chewers and non-chewers were significant ($p<0.000$).

Analysis of white lesions among study group (chewers) and control 1 (contralateral side of chewing) and group 2 (non-chewers) in terms of presence of white lesions

White lesions were significantly more frequent among the study group in comparison to both controls ($p=0.009$), and ($p=0.000$).

4.10.2 Multivariate analysis of the risk factors associated with white lesion

Table 14 shows the multinomial logistic regression model that was used to assess the risk factors that were significant at the univariate analysis. The results revealed that the risk factor that remained significantly associated with white lesion was qat chewing ($p=0.000$, OR= 23.480), water-pipe smoking ($p=0.002$, OR= 4.351) and cigarette smoking ($p= 0.039$, OR= 3.055)

When white lesions were correlated with the durations of chewing, water-pipe and cigarette smoking, the results were highly significant ($p=0.000$), water-pipe smoking was not significant ($p=0.260$), cigarette smoking was not significant ($p=0.368$).

Residence, oral hygiene, and tooth brushing behaviour were correlated with presence of white lesions. Results concerning residence were significant ($p=0.005$), oral hygiene was highly significant ($p=0.000$), and tooth brushing behaviour was not significant ($p=0.282$).

Table 14: Risk factors associated with white lesions

White lesions in oral side of chewing	95.0% C. I. for EXP(B)			
	Sig.	Exp(B)	Lower	Upper
Qat chewing	.000	23.480	8.093	68.118
Water-pipe smoking	.002	4.351	1.732	10.932
Cigarette smoking	.039	3.055	1.057	8.828
Duration of chewing, water-pipe smoking, cigarette smoking				
Chewing	.000	1.307	1.194	1.432
Water-pipe smoking	.260	1.067	.953	1.194
Cigarette smoking	.368	1.052	.942	1.176
Residence, oral hygiene and tooth brushing				
Residence	.005	3.527	1.473	8.447
Oral hygiene	.000	.015	.003	.085
Tooth brushing	.282	2.417	.480	12.181

5. DISCUSSION

In Yemen, qat chewing is a widespread social habit practiced by men, women and occasionally even children for few hours every day, and in many cases it is a lifetime habit. The continuous process of chewing qat leaves and keeping them in one side of the mouth until the cheek grows into a noticeable ball has been explained well in the literature. The literature of this study also covered qat history, botany, chemistry pharmacology and other related effects (2, 9, 26, 28, 31, 42, 53 and 64).

The adverse effects of this habit on different human body systems such as CNS, cardiovascular, digestive, genitourinary, and reproductive health systems were extensively investigated (7, 63, 74, 75, 82, 89 and 90).

The effects of qat chewing on different oral tissues including periodontal tissues, hard tissues of teeth, TMJ, muscles of mastication and salivary glands were also extensively reviewed (8, 12, 14, 91, 92 and 93).

The mechanism by which qat chewing induced white lesions on the oral mucosa might be due to its mechanical and/or chemical effects. The daily application of qat on the oral mucosa is expected to cause mechanical and/or chemical irritation leading to an increase in the thickness and keratinisation as a defence mechanism. Similar changes were reported under the traumatic focal (frictional) hyperkeratosis leading to increased thickness and colour changes of the oral mucosa due to continuous trauma (107).

Tannins, the phenolic compound present in qat, have some local effects on the digestive system, due to their astringent effects (8, 9). Moreover, they are known to cause an increase in the thickness of mucous membrane of the oropharynx and esophagus (81, 82). Also, chemical additives in qat green leaves such as chlorinated hydrocarbon from pesticides used in the treatment of qat plants (42). Both tannins and qat additives may have caused the changes seen in the oral mucosa.

On oral mucosa, oral keratotic white lesions with no leukoplakia or cancer have been reported to be due to qat chewing in many reports. Some degree of oral keratosis was found at the site of qat chewing among 60 Yemeni male chewers (14). Buccal and gingival white lesions at chewing sites were reported among Yemeni qat chewers who chewed for 3 years and more (12). 342 mild keratotic white lesions were reported

among Yemeni qat chewers (16). Also oral white lesions were reported among Yemeni Israeli Jew male chewers who had chewed qat for three years and more (100).

So far, all reports were either done on male chewers (14, 100) or included a very narrow sample of female chewers (12, 16). In the past, Yemeni women considered non-chewers, later on, few rich women used to chew qat, but the habit was hidden. Traditionally, chewing among females in Yemen was a shameful habit. Recently, chewing increased in women, but generally, they spend fewer hours in qat sessions and consumed smaller quantities than men (31).

This is the first survey conducted among Yemeni women qat chewers, with the objective of ascertainins a causal relationship between qat chewing and oral mucosal white lesions by applying a cross sectional study design. The role of cross sectional epidemiological method in ascertaining evidence for causal relationship is well established (104). Other advantages of cross sectional design are related to their usefulness in investigating exposures of fixed characteristics among individuals belonging to a specific socioeconomic situation or ethnicity. Its success was reported by many investigators who conducted studies on adverse health and habits relationship (104).

Qat consumption was the exposure hypothesized to produce an adverse effect on oral mucosa due to its physical and/or chemical action resulting in disease state among cases. To control for misclassification of the lesions, the investigator used the non-chewing sites of the jaw as control side (control 1). Non-chewers were used as second control. Although the investigator is aware of the fact that non-chewers are the best control, non-chewers of qat in Yemen are very rare. Because of this, the opposite side was used as a control side. This procedure minimizes the selection bias.

Subjects, exposed or non-exposed, were selected from patients seeking dental treatment in Sana'a city. Catchment area for patients who seek dental treatment in Sana'a city could be the city, surrounding villages or any area of Yemen. Majority of subjects, however, are expected to be from Sana'a city, thus forces driving both cases and control due to the same hospital are similar, and this also minimizes selection bias. Subjects who predominantly use one side of their mouths were selected, bilateral chewers were excluded. Predominant unilateral chewers may occasionally use other side, but the adverse effects are always greater on the chewing site. The majority of

Yemenis chew on their left sides. This is due to the need of the chewer to have the right hand free for use when necessary for writing and explaining.

In this study, 162 women had been recruited and divided into 109 chewers and 53 non-chewers. The mean age was 38.25 years, ranging from 20 to 65 years. No significant difference was found between qat chewers and control 2 (non-chewers).

The majority of the study population lived in towns 110 (67.9%) compared to 52 (32.1%) who lived in villages. No significant difference was found between the two groups. Similar results were reported among Yemeni male chewers (12).

The residence (town, village) was examined for correlation with white lesions. Findings showed that white lesions found among women living in town were higher than in women living in village. The difference was highly significant ($p=0.000$). This result was expected since women in town usually spend more time in their qat sessions compared to women in village (31).

The oral hygiene status (OHS) among the study population showed that 46 (28.4%) subjects had good OHS, 36 (22.2%) had fair OHS and the remaining 80 (49.4%) subjects had poor OHS. Tooth brushing among the study population was recorded in 105 (64.8%) subjects and the remaining 57 (35.2) did not brush their teeth. Type of device used for mouth cleaning among study subjects showed that 17 (16.2%) used miswak, 77 (73.3%) used toothbrush and paste and the remaining 11 (10.5%) used dental floss and other oral hygiene aids. Forty subjects (38.1%) brushed their teeth once, 60 (57.1%) twice, and 5 (4.8%) brushed their teeth more than twice a day.

The oral hygiene status was examined for correlation with white lesions. White lesions were predominant in women with bad oral hygiene ($p= 0.000$). This is probably due to the fact that 80 (49.4%) subjects who participated in this study had poor oral hygiene. Subsequently, superinfection with *Candida* spp. might have had an influence on the more whitish character of the lesions.

The presence of white lesions was correlated with residence, oral hygiene, and tooth brushing behaviour. Results were significant ($p=0.003$), oral hygiene was highly significant ($p=0.000$), and tooth brushing behaviour was not significant ($p=0.282$). Similar results regarding residence, oral hygiene, and tooth brushing behaviour was reported by AL-Sharabi (2002). In the latter study, 74% of subjects lived in town, 66% had poor oral hygiene status and 48% did not brush their teeth (12).

The age of starting chewing among the study population showed that 34 (31.2%) started chewing at 10-20, 52 (47.7%) at 20-30 and 23 (21.1%) at 30-40 years of age. Age of starting chewing was examined for correlation with white lesions. Findings were not significant ($p=0.339$).

The duration of the chewing habit ranged from 5 to 40 years with a mean of 14.79 years. The majority of chewers in this study chewed on their left side every day and for 3 - 6 hours per day. Similar results regarding the duration of the chewing habit per years, side of qat chewing in the mouth left or right, number of qat chewing days per week and also number of hours spent every day per chewing session has been reported (12, 16).

Results of our study showed that 21 (19.3%) subjects among cases were cigarette smoker, whereas 43 (39.4%) subjects were water pipe smokers. This result was expected because Yemeni women prefer water-pipe smoking to cigarette smoking during qat chewing (31). While male chewers in Yemen prefer cigarette smoking to water pipe smoking. In one study of male chewers, 55% were cigarette smokers and 7% were water-pipe smokers (12).

The most important result in this study was the detection of white lesions among Yemeni women due to qat chewing. Among cases, white lesions occurred in 82 (75%) subjects. White lesions occurred on the internal surface of the cheek at the side of qat chewing. From this side white lesions extended or continued to be present down along the lower buccal mucosa in 54 (65.8%) subjects and further continued to the vestibular sulcus in 36 (33.1%) subjects. Similarly, white lesions on buccal mucosa extended or continued to be present upward to the upper vestibular sulcus in only 3 (5.5%) subjects. White lesions present on gingival mucosa among cases were found in 28 (34.2%) subjects; white lesions present on gingival mucosa extended or continued to be present on alveolar mucosa in 15 (53.5%) subjects.

Among control 1 (non-chewing site), white lesions were detected in 6 (5.5%) subjects, extended to lower buccal mucosa in 3 (50.0%) subjects and extended further to lower vestibular sulcus only in 1 (33.4%) subject. On gingival mucosa, white lesions were detected in 3 (50.0%) subjects with no extension to alveolar mucosa. The presence of white lesions on buccal and gingival mucosa on the non-chewing site could be explained by the fact that some chewers chew a huge amount of qat and due to the

movement of chewing some fibres cross to the opposite side causing whitening or white lesions probably occurred due to the chemical effects of qat.

Among control 2 (non-chewers), white lesions detected in 7 (13.2%) subjects extended to lower buccal mucosa in 4 (57.2%) subjects and extended further to the lower vestibular sulcus in only 2 (50.0%) subjects. Gingival white lesions were recorded in 3 (42.8%) subjects, both of them extended to the alveolar mucosa. The presence of white lesions among non-chewer women could be explained by the fact that some females still regarded the qat chewing habit as shameful, so they either preferred not to report about it or these women were probably ex-chewers.

Presence of white lesions among non-chewers had been reported earlier in male subjects (12). Buccal white lesions were reported in 8.5% and gingival white lesions in 7.5% among non-chewers male subjects (12).

The results of white lesions in this study showed statistically highly significant differences between white lesions occurring among chewers (75%) when compared to those occurring in both controls (5.5%) ($p=0.000$), (13.2%) ($p= 0.009$). The results of white lesions reported in this study among Yemeni women qat chewers are in agreement with many studies done in Yemen on male qat chewers (12, 14, and 16). Results of this study are also in agreement with the study done in Israel on Yemeni Jew male chewers (100).

Regarding the etiology of white lesions, many people in the world conceptualized that qat is a form of tobacco or at least tobacco containing product. Thus, if it is so, it might be a cause of oral pre-cancer or cancer in Yemen. The only similarity between qat and tobacco is their alkaloid constituent. While the alkaloid in tobacco is nicotine, the alkaloid in qat is cathinone, i. e. the two products are obviously different. Tobacco smoking (cigarette or water-pipe) is well known to induce white lesions on oral mucosa (103, 105, 106). Tobacco related white lesions are known to develop into malignancy. Cigarette and water-pipe smoking is practiced frequently by qat chewers during chewing sessions. The white lesions detected among qat chewers could be due to the effect of tobacco use and not of qat chewing. White lesions detected in this study could not be attributed to qat chewing unless this effect of tobacco use is diminished or removed statistically.

In this study, white lesions detected among cases were statistically examined in correlation with qat chewing, cigarette smoking and water-pipe smoking. Statistical results of qat chewing were highly significant ($p=0.000$). In case of cigarette smoking, $p=0.039$ and in case of water-pipe smoking, p -value was 0.002. When the multinomial logistic regression model was used for the three groups, the relative risk (R.R.) or the odds ratio OR (95% CI) was 23.480 (8.093 - 68.118) in case of qat chewing, 3.055 (1.057 - 8.828) in case of cigarette smoking and 4.351 (1.732 - 10.932) in the case of water-pipe smoking.

White lesions among chewers were also statistically examined in correlation with the duration of chewing, cigarette smoking and water-pipe smoking. Statistical results of qat chewing duration was highly significant ($p=0.000$). In the case of smoking duration, the statistical result was not significant with $p=0.368$. Similar statistical result of water-pipe duration was not significant with $p=0.260$. Additionally, all white lesions recorded among cases ($n=82$) were found at the site of qat chewing. Differences between white lesions occurring among chewers in comparison to both controls were statistically highly significant ($p<0.000$).

All these statistical results support the hypothesis that white lesions reported in this study are attributed to qat chewing and not to tobacco. If these lesions were due to any type of smoking, they will be present anywhere in the mouth and not at the site of chewing.

In conclusion, qat chewing habit caused buccal and gingival white lesions at side of chewing among Yemeni women who chew every day for 3 - 6 hours and over a number of years. These results are reported for the first time.

6. ABSTRACT

BACKGROUND:

Qat chewing habit is widespread and practiced by millions of people in Yemen. The habit is increasing every year in Kenya, Somalia, Djibouti and Ethiopia. Recently, the habit is also increasing in Europe, where immigrants from qat consuming countries are living. An adverse health effect of qat chewing on different body systems and oral tissues has been reported.

AIM OF THE STUDY:

The aim of this study was to assess the association between habitual qat use and oral mucosal white lesions among Yemeni women.

STUDY DESIGN:

In a cross sectional hospital study, 162 healthy women were recruited. Subjects were divided into 109 qat chewers and 53 non qat chewers. Information obtained from the chewing sides among the 109 qat chewers was analyzed as cases. Two controls were used in this study. Information obtained from the opposite sides (non-chewing side) among the 109 qat chewers were analyzed as first control. Information obtained from both sides of the 53 non qat chewers was analyzed as a second control. Inclusion criteria were: healthy females aged ≥ 20 years, chewing qat continuously for a minimum of 5 years and on one side of their mouths only. Bilateral qat chewers, shammah users and subjects with poor general or mental health were excluded. All women were interviewed for qat chewing information and examined clinically for oral mucosal white lesions.

RESULTS:

Among chewers, white lesions were recorded in 82/109 (75.2%) at the chewing site. White lesions on the opposite side (control 1) were recorded among 6/109 (5.5%) subjects. White lesions among non-chewers were recorded in 7/53 (13.2%) subjects (control 2). White lesions were identified primarily on the lower buccal mucosa, vestibular sulcus, gingival mucosa, alveolar mucosa and upper vestibular mucosa on the chewing site. White lesions reported among chewers were positively correlated to

the side of chewing and to the longer duration of the habit. The difference in the prevalence of white lesions present among cases and both controls was highly significant ($p < 0.000$).

CONCLUSION:

Continuous chewing of qat fibres during sessions lasting 3 - 6 hours every day over decades caused mucosal white lesions, which were recorded on the chewing side among Yemeni women.

7. Zusammenfassung

Orale weiße Läsionen durch das Kauen von Qat bei Frauen im Jemen

Hintergrund:

Das Kauen von Qat ist im Jemen verbreitet und wird von Millionen Menschen praktiziert. Jedes Jahr steigt die Anzahl der Qat Konsumenten in Kenia, Somalia, Djibuti und Äthiopien. In den letzten Jahren lässt sich auch in Europa eine Zunahme dieses Habits durch Immigranten aus Ländern, in denen das Qat Kauen verbreitet ist, feststellen. Beschrieben wurden bereits Beeinträchtigungen einzelner Körpersysteme und Veränderungen des oralen Gewebes durch Qat bei Männern. Grund für Letzteres ist eine chemische und mechanische Irritation der Schleimhaut.

Ziel vorliegender Studie war es, mögliche Zusammenhänge zwischen dem Kauen von Qat und dem Auftreten oraler weißer Läsionen bei Frauen im Jemen darzustellen.

Material und Methode:

In einer Querschnittsstudie wurden 162 Frauen rekrutiert. Diese wurden in 109 Qat Konsumentinnen und 53 Nicht-Konsumentinnen eingeteilt. Als Kontrolle diente 1. die Schleimhaut der gegenüberliegende Seite der Qat Konsumentinnen (Kontrolle 1) und 2. die Schleimhaut bei Nicht-Konsumentinnen (Kontrolle 2). Einschlusskriterien waren gesunde weibliche Personen ≥ 20 Jahre, die seit mindestens fünf Jahren regelmäßig und nur auf einer Seite Qat kauen. Qat-Konsumentinnen, die auf beiden Seiten Qat kauten, Shammah-Gebraucherinnen sowie Personen mit schlechtem Allgemeinzustand wurden ausgeschlossen. Qat-Konsumentinnen wurden zu ihrem Habit befragt, alle Frauen wurden klinisch auf weiße Mundschleimhautläsionen untersucht.

Ergebnisse:

Bei 82/109 Qat-Konsumentinnen (75.2%) wurden weiße Veränderungen auf der Kauseite festgestellt. Weiße Veränderungen auf der gegenüberliegenden Seite (Kontrolle 1) wurden bei 6/109 (5.5%) Konsumentinnen beobachtet. Bei Nicht-Konsumentinnen wurden in 7/53 (13.2%) weiße Veränderungen nachgewiesen (Kontrolle 2). Weiße Läsionen wurden primär im kaudalen Bereich der Wangenschleimhaut, im Vestibulum, an der gingivalen Schleimhaut und im Vestibulum des Oberkiefers auf der Kauseite festgestellt. Es bestand eine signifikante Korrelation

zwischen dem Auftreten weißer Läsionen und der Kauseite sowie der Dauer des Habits. Der Unterschied der Häufigkeit des Auftretens weißer Läsionen zwischen Qat-Konsumentinnen auf der Kauseite und beiden Kontrollen war hochsignifikant. ($p < 0.000$).

SCHLUßFOLGERUNG:

Das Kauen von Qat während der täglichen 3 – 6-stündigen Qat-Sitzungen führte bei jemenitischen Frauen zu weißen Mundschleimhautläsionen auf der Kauseite. Das Entstehen von weißen Läsionen ist abhängig von der Dauer dieses Habits.

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9. APPENDICES

9.1. Figures



Figure 1 Qat majles



Figure 2 Women qat majles



Figure 3 Special female session of qat with water-pipe



Figure 4 Reclining against firm back cushion, resting left forearm on movable rest, left leg curled and right is perpendicular to the floor



Figure 5 Start qat chewing



Figure 6 Qat chewing left side of the mouth



Figure 7 Qat chewing left side of the mouth



Figure 8 Qat chewing right side of the mouth



Figure 9 Qat chewing, left side of the mouth



Figure 10 Qat branch with soft leaves



Figure 11 Qat tree



Figure 12 Large qat plantations



Figure 13 Qat terraces in Yemen



Figure 14 White lesions on left buccal mucosa

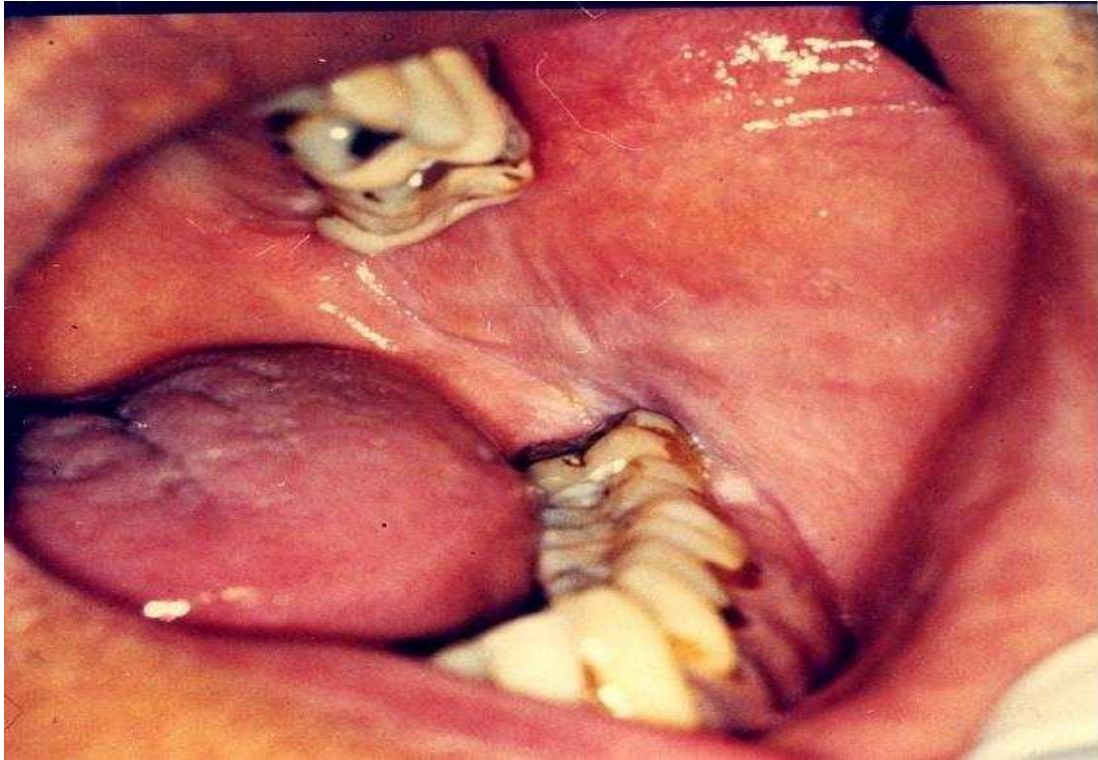


Figure 15 White lesions on left buccal mucosa and gingiva

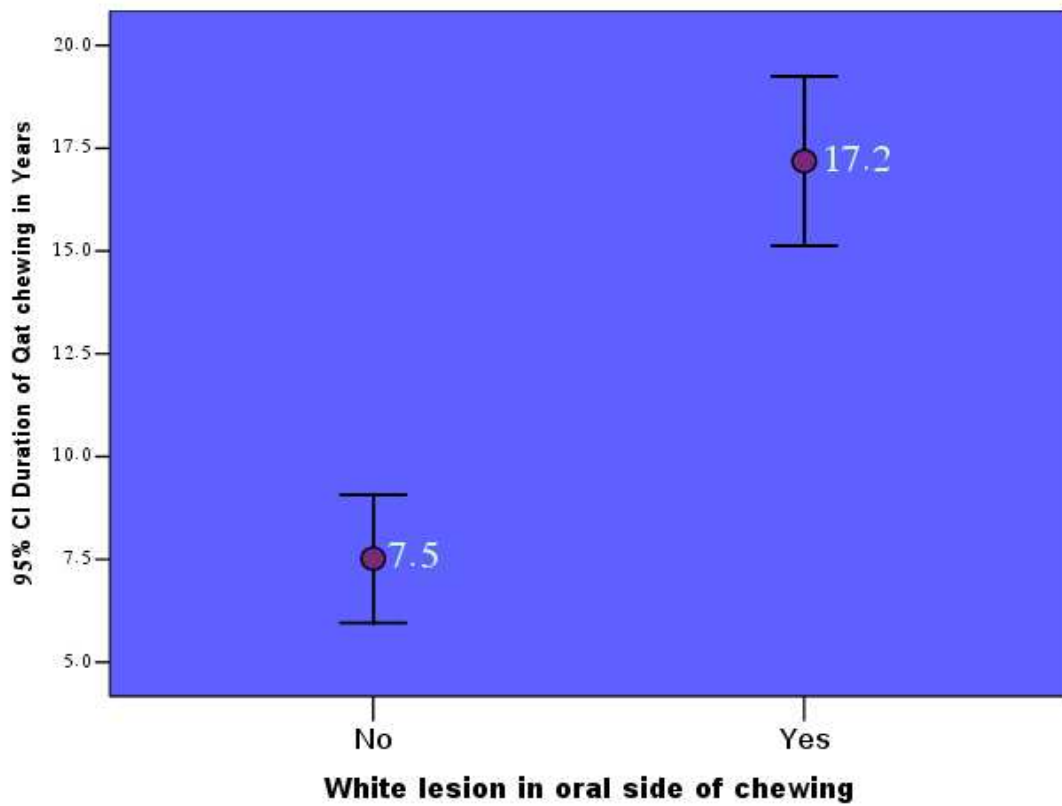


Figure 16 Duration of qat chewing in years for correlation with white lesions

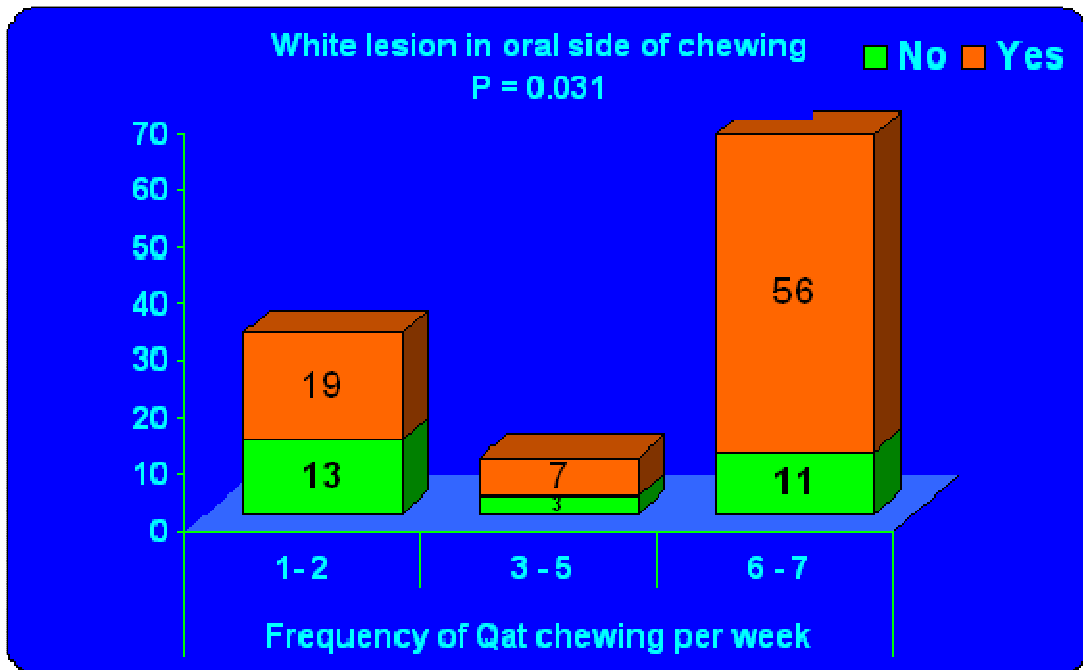


Figure 17 Frequency of qat chewing per week for correlation with white oral lesions on chewing side

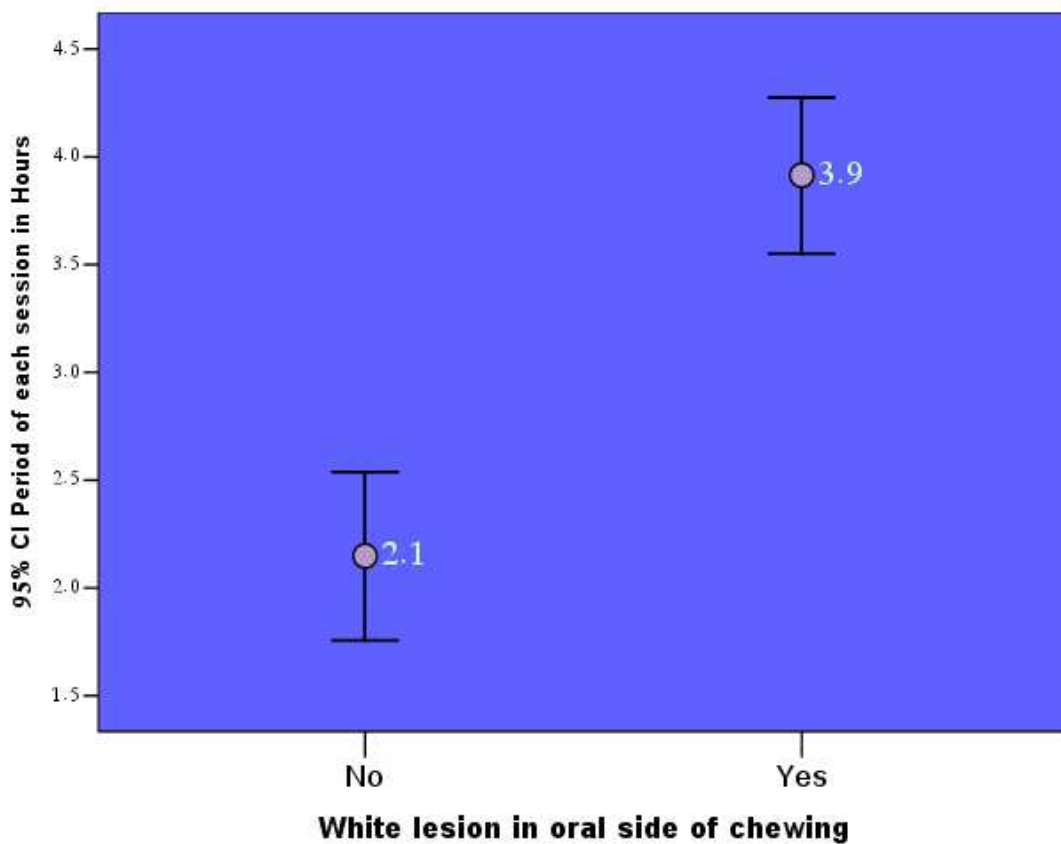


Figure 18 Period of each session in hours for correlation with white oral lesions on chewing side

9.2. Questionnaire format

Questionnaire to investigate Oral white lesions due to qat chewing among women in Yemen

Personal data:

Case No. □□□

Date □□ □□ □□

Name:

Forename:

Age □□

Birth day □□

Address:

Tel.

Medical history

Systemic disease: Yes No

If present explain:

Medicaments:

Information of qat

Chewers Non-chewers Duration of the habit in years □□

Age of starting qat chewing □□ Frequency of the habit per week □□

Period of each session in hours □□

Oral side of chewing: Right Left Bilateral

Other habits: Yes No

If yes, which habit?

.....

Information of cigarettes

Smoker Non-smoker With qat only

Duration of the habit in years □□

Number of cigarettes per day □□

Information of water-pipe smokers

Users Non-users With qat only

Duration of the habit in years □□

Frequency per day □□

Oral hygiene data

Sate of oral hygiene: Good Fair Poor

Tooth brushing: Users Non-users

Type of brush and O.H, aids: Miswak Toothbrush and paste

Dental floss and other aids

Frequency per day: Once Twice More than two

Intra-oral examination

Oral side of chewing:

White lesion: Yes No

Localization:

Opposite side: Yes No

Localization:

Photo date □□ □□ □□

Therapy

The first steps include patient counseling about the harmful side effects of qat to stop or withdraw this habit.

Outcome:

10. ACKNOWLEDGMENT

With much gratitude, I would like to pay tribute to my supervisor Prof. Dr. A. M. Schmidt-Westhausen at the Charité - Universitätsmedizin Berlin, Department of Oral Medicine, Dental Radiology and Oral Surgery in Germany. She has played an important role during the course of this study; her ideas, experience and constructive criticism, interest, and perspective of the field of white lesions, have always impressed me. Without her support, this study would not have been possible.

I wish to express my deep gratitude to the local supervisor Dr. Ali Kaid AL-Sharabi, Associate Professor of the Periodontology Faculty at the Dentistry University of Sana'a, for his support and guidance during this study.

I owe my particular thanks to everybody who helped me and made my mission easier in completing this study.

Finally, the special loving thanks go to my wife Hanan for her love and caring support as well as to my uncle Mr. Mohammed Musleh, his sons Saleh and Hisham and my brothers, for their support and understanding during these years.

This study was financially supported by a grant from the Faculty of the Dentistry Thamar University in Yemen (Grant No.147).

12. Erklärung

„Ich, Jabr AL-Sanabani, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: „Oral white lesions due to qat chewing among women in Yemen“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Berlin, 22. Juni 2010

Unterschrift