

# Think You Know all about oropharyngeal fibrosis? Secret role of Khat !!!

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## Abstract

**Objective:** The aim of this study is to show another possible cause of oropharyngeal fibrosis causing breathing difficulty and dysphagia, and to demonstrate the possible effects of Khat chewing on the pharynx and larynx. **Methods:** This cross-sectional study included all patients using Khat referred to Phoniatic Unit, Oto-Rhino-Laryngology department [removed for blind peer review] due to different reasons during the period of March-2017 and September-2019. A nine-question self-administered structured questionnaire was developed to covers all the socio-demographic factors in addition to Khat chewing habits. Full endoscopic evaluation was made and biopsies were obtained whenever possible. Patients were grouped into two groups; one using hot Khat (insecticide-irrigated) and the other using cold Khat (not insecticide-irrigated). **Results:** The overall sample was 120 cases; 22 are using hot Khat and 98 cold Khat. Both groups are comparable with regard age, gender, smoking, duration of using Khat as well as its frequency. Reasons for referral for clinic were different between groups ( $p < 0.001$ ). Oropharyngeal stenotic lesions are ( $p < 0.0001$ ) more frequent in the hot Khat group (77.3%) than in the cold Khat group (0%). In addition, chronic non-specific inflammation is significantly ( $p < 0.0001$ ) more frequent in the hot Khat group (68.2%) than in the cold Khat group (0%). **Conclusion:** The relation between Khat chewing and oropharyngeal fibrosis can be proposed with strong relation to the use of pesticides. Further studies are recommended to confirm this relation. **Succinct Key points:** Khat chewing, oropharyngeal fibrosis, dysphagia, nasal obstruction, Yamen

## Abstract

**Objective:** The aim of this study is to show another possible cause of oropharyngeal fibrosis causing breathing difficulty and dysphagia, and to demonstrate the possible effects of Khat chewing on the pharynx and larynx.

**Study Design:** Cross sectional study

**Setting:** Phoniatic Unit, Oto-Rhino-Laryngology department [removed for blind peer review]

**Participants:** This study included all patients using Khat referred to Phoniatic Unit due to different reasons during the period of March-2017 and September-2019.

**Main outcome measures:** A nine-question self-administered structured questionnaire was developed to covers all the socio-demographic factors in addition to Khat chewing habits. Full endoscopic evaluation was made and biopsies were obtained whenever possible. Patients were grouped into two groups; one using hot Khat (insecticide-irrigated) and the other using cold Khat (not insecticide-irrigated).

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more frequent in the hot Khat group (77.3%) than in the cold Khat group (0%). In addition, chronic non-specific inflammation is significantly ( $p < 0.0001$ ) more frequent in the hot Khat group (68.2%) than in the cold Khat group (0%).

**Conclusion:** The relation between Khat chewing and oropharyngeal fibrosis can be proposed with strong relation to the use of pesticides. Further studies are recommended to confirm this relation.

**Keywords:** Khat chewing, oropharyngeal fibrosis, dysphagia, nasal obstruction, Yamen

#### Introduction:

Oropharyngeal fibrosis can be a result of traumatic element as in fracture of larynx and pharynx following car accidents. Trauma could result also from operation as in adenoidectomy, tonsillectomy or after radiotherapy for head and neck carcinoma. Chronic specific infection can cause fibrosis, including syphilis, tuberculosis (specially lupus tuberculosis), diphtheria, occasionally measles, leprosy and chronic pemphigus<sup>1</sup>

Khat seems to affect the oral cavity and the digestive tract. A high frequency of periodontal disease has been suggested as well as gastritis and chronic recurrent subluxation and dislocation of the temporomandibular joint. Oral keratotic lesions at the site of chewing and plasma cell gingivitis (allergic reaction to Khat) have been reported.<sup>2-5</sup>

Three plants are recognized for their psychostimulant effects; they are Ephedrine, Cocaine, and the Khat. The latter, the Khat, produces cathinone; an intermediate metabolite, and derivatives of cathinone are an emerging class of new psychoactive substances. Khat qat, q'at, kat, kath, gat, chat, tschat (Ethiopia), miraa (Kenya) refer to the leaves and the young shoots of tree *Catha Edulis* Forsk.<sup>6-8</sup>

Across Europe, the use of khat is low. Khat use is limited to countries with immigrant communities from countries where khat use is common (such as Ethiopia, Somalia, Yamen and Kenya). The most recent estimates suggest that Europe accounts for about 40% of the khat seized worldwide. The use of Khat has significantly increased in Europe in the past 20 years with the appearance of its different systemic side effects<sup>9</sup>. Figure 1 showing Countries among EU Member States and Norway not specifically controlling khat under drugs laws, and estimates of khat seizures.<sup>10</sup>

There are no legal restrictions on cultivation, use, or age limits of use of Khat in Yemen, Ethiopia, Djibouti, Somalia and Kenya. For example, in Yemen, 15–20% of children under 12 years use Khat<sup>11</sup>. The distributions of Khat consumption in the African horn and close by countries are shown in Figure 2<sup>12</sup>.

Khat is consumed by chewing its fresh young leaves and twigs. The exudate is swallowed, and the residue spat out. In a typical single chewing session, 100–500 gm of Khat over 3–4 h can be consumed.<sup>13-17</sup>. The pattern of absorption of cathinone, cathine, and norephedrine in humans shows a two-compartment model with a two-segment absorption; the buccal mucosa is the first site of absorption and the small intestine the second site<sup>18</sup>. Fresh Khat has mood-enhancing properties similar to amphetamines. In the user, consumption of fresh Khat produces feelings of euphoria, alertness, energy, and confidence. It also causes loquacity, appetite suppression, insomnia as well as sympathomimetic effects hypertension, tachycardia, hyperthermia, mydriasis – to which tolerance can develop.<sup>13</sup>

The tannins present in Khat leaves are held responsible for the observed gastritis<sup>19</sup>. Moreover, **Makki (1975)**<sup>20</sup> stressed the importance of Khat when she found that most of the oral squamous cell carcinomas of her study patients were located in the buccal mucosa and lateral sides of the tongue, which comes into direct contact with the Khat during chewing. Also, many authors stressed the correlation between Khat chewing and oral squamous cell carcinoma.<sup>21,22</sup>

One important observation about Khat is that West to Sanaa' city in Yemen is a new area for harvesting Khat in the past 30-40 years. Junko et al. (2010[23])<sup>23</sup> proved that areas west to Sanaa' city needed organic phosphorous insecticide to grow the Khat. Also, areas north to Sanaa' city have natural Sulphur; mandatory to Khat growing. Other regions in Yemen do not use organic phosphorous insecticide.<sup>24</sup>

The rationale intended for this current study was to explore the relation between the types of Khat; hot (spicy: insecticide-grown) or cold as a cause of oropharyngeal fibrosis seen as a pattern in Khat chewers.

## Subjects and Methods

The current study was a descriptive cross-sectional study that included all patients using Khat referred to Phoniatic Unit, Oto-Rhino-Laryngology department, Faculty of Medicine, [removed for blind peer review] due to different reasons during the period of March 2017 and September 2019. The patients are found to be from Yemen and all are found to have the habit of Khat chewing.

The objective of the study was explained to the study participants. All participants included in the study have provided an oral consent. We did not believe that the questionnaire provided to patients compromises ethical principles. The Ethical Review Board of the faculty of Medicine-has approved this study.

Patients with history of head and neck trauma, (surgical, physical), patients with cleft palate and patient with granulomatous lesions (Leprosy, TB, scleroma or syphilis) were excluded from study.

A nine-question self-administered structured questionnaire consisting of open and closed ended questions was developed from a review of the literature and translated into the Arabic language, the official language of Yemen, by an expert translator fluent in both English and Arabic. The questionnaire covers all the socio-demographic factors in addition to Khat chewing habits. The questionnaire was anonymously responded.

Full evaluation was done under the protocol of voice assessment in [removed for blind peer review] using Flexible naso-endoscope with distal chip (Henke Sas Wolf) and biopsies were obtained whenever possible. <sup>25</sup>

The patients were grouped into two groups; one using hot Khat (insecticide-irrigated) and the other using cold Khat (not insecticide-irrigated). Both groups were compared for all demographic variables as well as clinic-pathologic variables.

Recorded data were coded, entered, cleaned, and analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean  $\pm$  standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square ( $\chi^2$ ) test of significance was used in order to compare proportions between two qualitative parameters. Bivariate analyses, Chi-square test or t-test according to the type of the data, were carried out to examine the relationship between the outcome variable of Khat chewing and selected determinant factors. The confidence level was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant if  $< 0.05$ .

## Results

The overall sample was 120 cases; 22 are using hot Khat and 98 cold Khat. All patients in the hot Khat group are from Sanaa and west regions while all of the cold Khat group are from areas north to Sanaa. The questionnaire used in this study was validated and the Cronbach alpha was 0.847.

### Demographic characteristics of both groups

Both groups, hot Khat and cold Khat groups are comparable with regard the age and gender. The mean age was  $24.71 \pm 5.72$  and  $23.2 \pm 4.54$  years in the hot Khat group and the cold Khat group, respectively (p-value = 0.182). The males are more than females in both groups; 68.2% & 78.6% in hot and cold Khat groups, respectively (p-value = 0.402) (Table 1).

### Smoking and Khat chewing habits in both groups

The majority  $> 95\%$  in both groups are smokers. Patients from the hot Khat group were using it for a duration of  $7.3 \pm 2.4$  years while those of the cold Khat using it for a duration of  $6.9 \pm 1.7$  years, (p-value = 0.647). The majority of patients 90.9% in hot Khat group and 86.7% in cold Khat group were using Khat more than twice per day, (p-value = 1.000), as shown in Table 1.

### Clinical characteristics in both groups

There is a significant ( $p$ -value  $< 0.001$ ) difference in the reasons for referral for clinic in both groups. The most frequent reason for referral to clinic in the hot Khat group is difficulty in nasal breathing, oral & nasal breathing followed by phonoasthenic symptoms; mentioned by 36.4%, 31.8% and 22.7%, respectively. While, in the cold Khat group it is phonoasthenic symptoms, aspiration followed by difficulty in oral and nasal breathing; mentioned by 57.1%, 21.4% and 19.4%, respectively, (Figure 3 & Table 1)

Also, oral sores or sore throat are more frequent in the hot Khat group (90.9%) than in the cold Khat group (13.3%), ( $p$ -value  $< 0.0001$ ).

Endoscopic and histopathologic examination in both groups

Oropharyngeal stenotic lesions are significantly ( $p$ -value  $< 0.0001$ ) more frequent in the hot Khat group (77.3%) than in the cold Khat group (0%); whereas, laryngeal and vocal folds affections are more frequent in the cold Khat group (55.1%) than in the hot Khat group (0%), as shown in Table 2 and Figures 4 & 5. Also, chronic non-specific inflammation is significantly ( $p$ -value  $< 0.0001$ ) more frequent in the hot Khat group (68.2%) than in the cold Khat group (0%), as shown in Figures 4 & 5.

Discussion:

This current cross-sectional study aimed to investigate the relation between pesticide use in Khat irrigation and oropharyngeal fibrosis (stenosis). Only from this study, we want to develop a hypothesis that can be further tested which may help in the understanding of the Khat chewing habit and its hazards on the human health and can answer for cases described as "idiopathic oropharyngeal stenosis".

The results of this study showed that there is a significant difference between those using Khat irrigated by pesticides (hot Khat) and those using Khat not irrigated by pesticides (cold Khat) in the reasons for referral for clinic. The most frequent reason for referral to clinic in the hot Khat group is difficulty in nasal breathing, difficulty in oral & nasal breathing followed by phonoasthenic symptoms. While, in the cold Khat group it is phonoasthenic symptoms, aspiration followed by difficulty in oral and nasal breathing. Also, oral sores or sore throat are more frequent in the hot Khat group than in the cold Khat group.

Moreover, the endoscopic and histopathologic examination in both groups are different. Oropharyngeal stenotic lesions with almost normal larynx are significantly more frequent in the hot Khat group than in the cold Khat group; whereas, laryngeal and vocal folds affections are more frequent in the cold Khat group than in the hot Khat group. Also, chronic non-specific inflammation is significantly more frequent in the hot Khat group than in the cold Khat group.

Those aforementioned results can help to develop a hypothesis that needs further testing which is that the pesticides used in irrigation of the Khat may play a significant role in the pathogenesis of certain lesions in those people chewing Khat.

The main salient feature in all presented hot Khat chewers are the fibrosis which starts from the oropharynx (velum and faucial pillars) and extending till the hypopharynx and supralaryngeal structures (those are the sites that the Khat juice reaches during chewing) and also most of the Khat chewers were found to have normal glottis (this is the only place that is not involved in Khat juice swallowing).

Some patients suffered from dysphagia due to fibrosis in the upper esophageal segment and underwent esophageal balloon dilatation. They are in direct contact with pesticide as some of them are pesticide merchants.

The present results of histopathological studies show the presence of chronic inflammatory cells which may be the cause of the present fibrosis which may be due to prolonged irritation. The mechanical and chemical irritation together with the high level of DDT founded in Khat leaves is the possible cause of the present fibrosis in the oropharynx and upper part of esophagus. That is because DDT are widely used to increase crop outputs to improve the quality of products, and to decrease the incidence of illness propagated by insects such as malaria and typhus as proved by Beceiro et al. <sup>26</sup>

Moreover, the study of Junko showed that chewers of Khat produced in fields where pesticides are used have more symptoms than chewers of Khat produced in fields where pesticides are never used or used rarely.<sup>23</sup>

Some of the presented patients stated that they can differentiate between types of Khat that been irrigated with water containing pesticides and the ones that been irrigated by natural water. Most of the patients stated that they do not usually wash the Khat prior to its use. This can explain the reason why Khat can cause such changes in few cases among millions of Khat chewers all around Yemen.

### Conclusion:

The relation between Khat chewing and vocal tract tissue reaction leading to oropharyngeal fibrosis and deformities could be proposed with strong relation to the use of pesticides. Further studies are needed to confirm the relation between different types of pesticides and Khat chewing. Wide sample of control group in areas north to Sanaa' and areas in Sanaa' or to the west with analysis of the type of Khat in each area and with oro-pharyngo-laryngeal examination of these cases. Strong recommendations to stop using Khat irrigated with Pesticides or at least to wash it carefully to wash out the pesticide remnants. Questions regarding Khat chewing should be involved in clinical history taking especially in immigrants coming from countries famous of using Khat.

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Table 1: Demographic data and patients’ characteristics

	Hot Khat N = 22	Cold Khat N = 98	P-value
Age, mean (SD) [minimum-maximum]	24.71 (5.72) [18-45]	23.2 (4.54) [18-46]	0.182
Gender			
Males	15 (68.2)	77 (78.6)	0.402
Females	7 (31.8)	21 (21.4)	
Smoker	21 (95.5)	94 (95.9)	
Region			
Sanaa and west	22 (100)	0 (0.00)	P < 0.001
North to Sanaa	0 (0.00)	98 (100)	
Duration of using Khat			
Years	7.3 (2.4)	6.9 (1.7)	0.647
Times per day			
Twice	2 (9.1)	9 (9.2)	1.000

	Hot Khat N = 22	Cold Khat N = 98	P-value
More than twice per day	20 (90.9)	85 (86.7)	
Main reason for referral to clinic			
Aspiration	1 (4.5)	21 (21.4)	< 0.001
Dysphagia	1 (4.5)	1 (1.0)	
Nasal obstruction	8 (36.4)	1 (1.0)	
Oral and nasal obstruction (difficult breathing)	7 (31.8)	19 (19.4)	
Phonasthenic symptoms	5 (22.7)	56 (57.1)	
Signs of chewing			
Oral sores or sore throat	20 (90.9)	13 (13.3)	P < 0.001

Table 2: Gross and histopathologic examination

	Hot Khat N = 22	Cold Khat N = 98	P-value
Gross examination			
Laryngeal and vocal folds affection	0 (0.0)	54 (55.1)	< 0.001
Deformed epiglottis	22 (100)	0 (0.0)	
Oropharyngeal stenosis	17 (77.3)	0 (0.0)	
Esophageal stenosis	2 (9.1)	0 (0.0)	
Histopathologic examination			
Chronic non-specific inflammation	15 (68.2)	0 (0.0)	< 0.001
Laryngeal polyp	0 (0.0)	33 (33.7)	
Did not undergo biopsy	7 (31.8)	65 (66.3)	

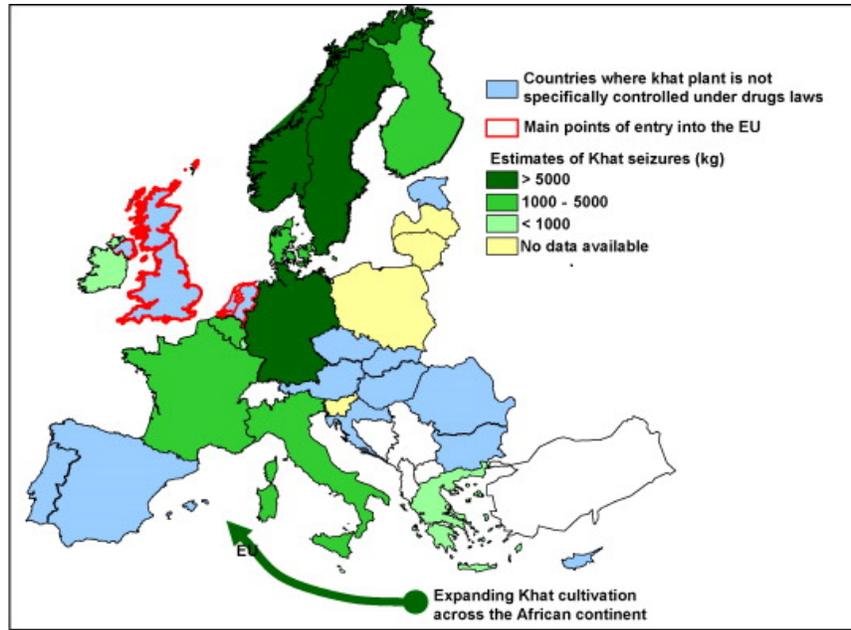
Figure 1: Countries among EU Member States and Norway not specifically controlling khat under drugs laws, and estimates of khat seizures. **Source: EMCDDA (2009)**

Figure 2: The estimated percentage of Khat users in the different countries and regions of southwestern Arabian Peninsula and eastern Africa (sourced from various publications (Horn of Africa map (2018)-[http://d-maps.com/carte.php?num\\_car=&lang=en](http://d-maps.com/carte.php?num_car=&lang=en)). (Patel 20199)

Figure 3: Reasons for referral to phoniatic unit

Figure 4: Endoscopic picture and histopathologic examination of some cases: part 1

Figure 5: Endoscopic picture and histopathologic examination of some cases: part 2



Source: EMCDDA (2009c).

