Les effets de l'usage du narguilé sur l'etat bucco-dentaire

Oral health effects associated with narghile use

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RÉSUMÉ

Introduction: Comme les dentistes rencontrent incontestablement des fumeurs de narguilé parmi leurs patients, il est important de les informer des effets néfastes potentiels de ce mode de tabagisme sur l'état bucco-dentaire.
Objectif: Rapporter les effets de l'usage chronique du narguilé sur l'état bucco-dentaire.
Méthodes: Source des données. Le moteur de recherché "PubMed" a été consulté jusqu'au 30 Juin 2015 sur les effets chroniques de l'usage du narguilé sur l'état bucco-dentaire. Les termes («lesion orale», «cancer oral», «alvéolite» ou «parodonte») et («narguilé » ou ses différents synonymes) ont été utilisés.
Sélection des études. Seuls les études originales et les cas ou séries de cas axés sur l'être humain ont été inclus. Seize études répondaient aux critères de sélection mais seules 14 ont été retenues.
Extraction des données. Les données, récoltées par deux auteurs, ont été résumées dans des tableaux. Toutes les données, y compris le type d'étude et les résultats, ont été analysées conjointement par les quatre auteurs.
Résultats : Synthèse des données. L'usage du narguilé a des effets nocifs sur l'état buooc-dentaire. Ces effets sont dominés par les maladies parodontales, les alvéolites et les lésions oro-muqueuses.
Conclusion: L'usage chronique du narguilé engendre des effets nocifs sur l'état bucco-dentaire. Cette étude appuie la nécessité d'une réglementation plus stricte concernant ce mode de tabagisme.

Mots-clés
Tabac - Lesion orale - Cancer oral - Parodonte - Alvéolite

SUMMARY

Background: As dentists are certain to encounter narghile-smokers amongst their patients, it is important to inform them of the possible detrimental impacts of narghile-use on oral-health.
Objective: To review the literature on the oral-health effects of narghile-use.
Methods: Data sources. We made a search on PubMed until June 30th, 2015 for the chronic oral-health effects of narghile-use using the terms "oral-lesions" or "oral-cancer" or "dry-socket" or "periodontium" and 'narghile' or its different synonyms.
Study selection. Only original studies and case reports or series focusing on clinical human studies were included. Sixteen studies met the selection criteria and 14 were retained.
Data extraction. Data were abstracted by two authors and summarized into tables. Abstracted data, including study type and results, were analyzed jointly by four authors.
Resultats : Data synthesis. Narghile-use has harmful effects on oral-cavity including periodontal diseases, dry-sockets and oral-mucosa lesions.
Conclusion: Narghile-use is associated with a variety of adverse long-term oral-health effects that should reinforce the need for stronger regulation.

Key-words
Tobacco - Oral lesions - Oral cancer - Periodontium - Dry-socket

Tobacco-use is the major cause incremented in killer diseases and there is a need to study the trends and patterns of its different forms(1-3). During the preceding years, there has been a raising trend in the use of a special form of tobacco, namely narghile-use(4, 5). This tobacco-use mode is gaining popularity in several regions such as North-Africa, Asia and the Middle-East(1-12). For example, male narghile-smokers (NS) represent respectively 22% in Egypt, 50% in Syria and 57% in Kuwait(5, 8, 9).

The public opinion, and especially the medical world, usually underestimate the damaging effects of narghile-use, despite its dangerous effects on health(3-5, 13-16). In a recent study aiming at exposing its perception among university students (n=1255), it was found that 6.3%, 33.0% and 12.1%, respectively, believe that narghile-use is not harmful; think that the carcinogenic chemicals are filtered while narghile smoke passed from the water and believed that «narghile smoke contains no nicotine» statement was true(13). Indeed, it has been proven that its smoke is rich in hundreds of substances potentially hazardous to health, and some of them are classed as carcinogens and/or tumor promoters(3, 13, 15-21). Furthermore, compared to cigarette-smoke, narghile-smoke has a higher level of nicotine, carbon-monoxide and tar(7, 18, 21). Narghile-use is frequently associated with several diseases(18, 21-28) and numerous reviews were published concerning its general effects on health (3, 4, 14-16, 29-43). However, to the finest of authors' awareness, no specific review has evaluated its effects on oral-health. As dentists are generally certain to come across NS amongst their patients, it is mandatory to inform them of the significantly damaging impacts of narghile-use on oral-health.

In a recent "Letter to Editor"(44), strengths as well as flaws associated with the methodology of studies aiming at evaluating some effects of narghile-use on oral-health(45-58), were described. The present paper is a narrative review of the current knowledge on the oral-health effects of narghile-use.

METHODS

Eligibility criteria

For a comprehensive assessment of published data on the narghile-use effects on oral-health, a restrictive approach of study inclusion was assumed. All available original clinical studies, case reports or case-series were included. Publications that did not comply with the present study purpose as well as editorials and letters to editor were excluded. Only articles written in English were eligible.

Search strategy

PubMed database was searched, using previously reported strategies (3, 29), from the earliest studies of those databases until June 30th, 2015. The PubMed search was carried out through the following terms "oral-lesions" OR "oral-cancer" OR "dry-socket" OR "periodontium" AND 'narghile' or its different synonyms(3, 15, 16, 29, 39): Arghil OR Arghila OR Arghileh OR Argil OR Argileh OR Borry OR Chicha OR Chichi OR Chilam OR Ghelyan OR Ghoza OR Goza OR Gozha OR Guza OR Hooka OR Hookah OR Hubbl Bubbl OR Hubbl-Bubbl OR Hubble Bubble OR Hubble-Bubble OR Hukka OR Huqqa OR Nargeeleh OR Narghil OR Narghile OR Nargil OR Narguile OR Narguilé OR Narguileh OR Narguilhé OR Sheesha OR Shisha OR Shui yan dai OR Water Pipe OR Waterpipe OR Water-Pipe).

Selection process

The studies were selected based on the eligibility criteria described previously. Titles and abstracts resulting from Pubmed search were screened. Then, the full texts of citations considered as potentially eligible were obtained. Finally, the full texts were screened for eligibility. *MK* and *HBS* (in the authors' list) performed PubMed research and collected published papers.

Data abstraction

Each included study was reviewed thoroughly and the selected studies were organized and summarized into tables prior to analysis. The abstracted data included narghile-use long-term effects on oral-health and the outcomes.

Data analysis

The four authors analyzed the data according to their medical experience and knowledge. The studied populations and their demographic characteristics, the study design and the methodological flaws were mentioned in a recent "Letter to Editors"(44). Study results were presented in the context of all other available evidence.

RESULTS AND DISCUSSION

Collected data

Studies aiming at evaluating the effects of narghile-use on oral-health(45-58) have collected the following parameters (Tables 1-4): *i)*

Clinical data**:** plaque-index; gingival-index; plaque%; gingival-bleeding; probing-pocket-depth (PPD); clinical-attachment-loss (CAL); dry-socket; suspicious-lesions and oral-cancer; ii)

Radiological data: periodontal-bone-height (PBH); bone-loss; vertical-bone-defect; and **iii)**

Biological data: periodontal-microflora; tail-moment; tail-length; %Tail DNA; fragmented DNA; nuclear-size; cytoplasmic-size; nuclear/cytoplasmic ratio; feret-ratio; micronuclei; total-number-of-micronuclei; number-of-cells-containing- micronuclei. The above collected data

Table 1. Results of studies aiming to evaluate the effects of narghile-use on periodontal-health (clinical studies).

1er author	Bilsara(58)												Natto(54)				Natto(55)			
	PD	PI%			GI%		PPD%			CAL%		GB%	PI	GI	Plaque%	GB%	PI	GI	PPD	PD
		0.1-0.9	1-1.9	2-3	0.1-0.9	1-1.9	>3	>4	>6	>1	>3									
Narghile-smokers (NS)	24[†]	38	33	31	6	94	37±3[a] †	37±3[a] †	15±2[a]	21±3[a] †	16±2[a]	66±3[a†]	1.6 [1.5-1.8][a†‡]	1 [0.8-1.2][a†]	65% [50-80][a]	37% [31-42][a†]	1.6 [1.5-1.8][a†]	1 [0.9-1.2][a]	3.1 [2.9-3.2][a†‡]	30[†]
Cigarette-smokers (CS)	43	39	43	28	13	87	30±4[b]	29±4[b]	11±3[b]	14±4[b]	10±4[b]	58±5[b]	1.1 [0.9-1.3][b]	0.9 [0.8-1][b]	69% [62-77][b]	29% [23-36][b]	1.1 [0.9-1.3][b]	0.9 [0.8-1][b]	3 [2.9-3.2][b]	24
Mixed-smokers (MS).	29	26	40	34	10	90	35±3[c]	34±3[c]	12±2.3[c]	26±3[c]	22±5[c]	63±4[c]	1.3 [1.1-1.5][c]	1 [0.8-1.1][c]	75% [67-82][c]	31% [24-38][c]	1.3 [1.1-1.5][c]	1 [0.8-1.1][c]	2.6 [2.5-2.8][c]	17
Never-smokers (Non-S).	13	42	39	16	5	95	19±4[d]	19±4[d]	6±3[d]	3±4[d]	2±3[d]	46±5[d]	0.7 [0.6-0.8][d]	0.6 [0.5-0.7][d]	40% [34-45][d]	24% [20-27][d]	0.7 [0.6-0.8][d]	0.6 [0.5-0.7][d]	2.3 [2.1-2.5][d]	5
	.Overall prevalence of PD: 25.6%. .After adjusting for age, CS, NS and MS were significantly more likely to have PD (OR respectively, 4.8; 4.3 and 4.8). .No significant differences in the OR of PD between the 4 groups of smokers.												.NS exhibited the highest PI level. .Correlation between Plaque% and GB% was lower in NS than Non-S.				.PPD per person: 2.8 [2.7-2.9][a] .PPD increase with age .PD prevalence increased risk is significantly associated with smoking, PI, GI.			

CAL: clinical-attachment-loss. GB: gingival-bleeding. GI: gingival-index. OR: odds-ratio. PD: periodontal-disease. PI: plaque-index. PPD: probing-pocket-depth.
Data are mean±SD* or mean [95% confidence interval][‡] and prevalence for PD.
Significant differences: [a]NS vs. CS. [b]NS vs. Non-S. [c]NS vs. MS.

are extensively detailed in the **Supplementary data section**.

Narghile-use has harmful effects on the mouth including periodontal diseases, dry-socket and oral-mucosal lesions (Tables 1-4). The oral harmful effects of narghile-use highlighted in this review are part of a more general phenomenon(3, 4, 14, 16, 29).

Effects on periodontal-health

Tables 1 and 2 display the effects of narghile-use on periodontal tissues(53-58). The periodontal-health was evaluated according to clinical data (plaque-index, gingival-index, gingival-bleeding, PPD, CAL and plaque%)(54, 55, 58), radiological measurements (vertical-bone-defect and PBH)(53, 56) and microbiological sampling such as periodontal-microflora(57).

Clinical data: The effects of narghile-use on plaque-index are controversial. While plaque-index mean values were significantly higher in NS compared to cigarette-smokers (CS) or mixed-smoker (MS, cigarette and narghile) or healthy-subjects-never-smokers (Non-S)(54), or compared only to Non-S(55), no statistical significant difference was found between percentages of subjects having plaque-index ranges (plaque-index%) among the four groups(58). In addition the plaque% seems to be (statistical comparison not performed) higher in NS compared to Non-S(54).

The effects of narghile-use on gingival-index were also controversial. While one study(54) found gingival-index mean values of NS to be altered compared only to Non-S, two others(55, 58) found similar gingival-index mean values(55) and similar percentages of subjects having gingival-index ranges (gingival-index%)(58) in the four groups.

It seems that narghile-use alters the gingival-bleeding with two studies (54, 58) reporting statistical significant difference between the NS and the Non-S groups.

Narghile-use alters the PPD with NS group having higher values compared to Non-S(55, 58) or to MS(55) groups. The prevalence of periodontal diseases in NS was significantly higher than that of Non-S in two studies(55-58). It seems that narghile-use alters CAL with significantly higher percentages of NS having CAL ranges (CAL%) than those of Non-S group.

A part from the methodological limitations previously highlighted elsewhere(44), the discrepancy between results could be explained by different clinical approaches: clinical recordings in all teeth except the third molar(56) or in only six representative teeth(58).

Radiological data: Narghile-use seems to alter the bone height. On the one hand, the prevalence of vertical-bone-defect was significantly higher in the NS group when compared to the Non-S one(53). On the other hand, the PBH mean values of the NS group was significantly lower than those of Non-S and MS groups(56) and the prevalence of bone-loss in the NS group was significantly higher than in the Non-S one(56).

Microbiological samples: The subgingival bacterial profiles were independent of narghile-use(57). This is not in accordance with Ge et al.(59) who observed that the differences in periodontal-microflora structure between deep and shallow sites revealed by cluster analysis, was influenced by patient-level effects such as smoking cigarettes.

Biological mechanisms responsible for the effect of narghile-use on periodontal health: The biological mechanisms responsible for the effect of narghile-use on periodontal health are not elusive. According to Natto et al.(55, 56), the impact of narghile-use on periodontal health is caused by the inhalation of toxic substances. Furthermore, the levels of nicotine and its principal metabolite cotinine increase in saliva among NS(60). Other hypotheses such as the increase of matrix-metalloproteinases expression may be suggested(61). Matrix-metalloproteinases are the key enzymes which have been associated with periodontal inflammation and play an important role in the degradation of the host tissues that support the teeth(61).

Dry-socket

Dry-socket is the most common complication after tooth extraction(62). Its cause has yet to be firmly established(63). Only one study(46) reported that narghile-use increased the incidence of dry-socket after the removal of the third mandibular molar compared to Non-S (Table 3). One possible explanation, given by Al-Belasy et al.(46) was that substances in tobacco and its smoke, particularly nicotine, cotinine, carbon-monoxide, and hydrogen cyanide, are cytotoxic to a number of cells and inhibit wound repair. Nicotine, the active drug in smoke, increases platelet adhesiveness, raising the risk of thrombotic microvascular occlusion and tissue ischemia(64). It also inhibits the proliferation of fibroblasts and macrophages(64). Hydrogen cyanide inhibits the enzyme systems operative in oxidative metabolism and oxygen transport at the cellular level(64). carbon-monoxide forms carboxyhemoglobin in the blood, resulting in decreased oxygen transport and changes in vascular endothelium characteristic of endarteritis obliterans(65). Smoking is also associated with endogenous catecholamine release, resulting in vasoconstriction and decreased tissue perfusion(66). Conceivably, the heat from the burning tobacco, the introduction of a foreign substance that could act as a contaminant in the surgical site, and the suction applied to the cigarette, which might dislodge the clot from the alveolus and interrupt healing, are further local considerations(62).

Table 2. Results of studies aiming to evaluate the effects of narghile-use on periodontal health (radiological and microbiological studies).

1st author	Natto(56)		Natto(57)																				Baljoon(53)	
Results	PBH	BL	Pm		Td		Pn		Pi		Si		Tf		Aa		Fn		Pg		Cr		Ec		Sn		Vertical-defect (VD)	
			PPD																									
			<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	<6	≥6	Prevalence	Severity
NS	76% (75- 78)[b][c]	27[a]	92	97	75	91	97	71	79	65	79	59	42	71	42	59	42	47	17	47	17	38	29	6	0	12	47[a]	26% [19-33][b]
CS	76% (74- 78)[b]	24	100	90	73	95	63	40	80	45	80	45	53	65	20	75	53	50	40	45	6	35	20	10	13	0	54	28% [17-38][b]
MS	80% (79- 82)[b]	9																									33	19% [11-28][b]
Non-S	81% (792-83)[b]	6	93	100	64	60	93	80	61	70	61	70	53	80	50	40	44	20	39	40	20	0	11	0	3	0	23	13% [06-2][b]
	.PBH decreases with age. .Relative risk of BL (after adjustment for age) associated with NS (3.5-fold) and CS (4.3-fold) compared with Non-S.		.PM prevalence did not significantly differ with age with the exceptions of Cr at score 1 cut-off (contrast colonized Vs. non-colonized individuals) and Tf at score 3 cut-off (contrast heavily colonized Vs non-colonized and less heavily colonized individuals). .PM prevalence did not differ between sexes neither at score 1 nor score 3 cut-off. .At score 1 cutoff, PM prevalence was significantly higher in individuals with sites ≥6 compared to those with sites <6 for Td and Aa. .At score 3 cut-off, PM prevalence was significantly higher in individuals with sites≥6 compared to those with sites<6 for Td, Pn, Si, Tf and Aa. .No statistically significant differences between smokers groups for any one of the organisms with the exception of Td at score 1 cut-off where the prevalence was significantly higher in NS compared to Non-S. .At score 1 cutoff, smoking was not associated with an increased risk of detecting the microorganisms studied. .At score 3 cut-off, an increased risk of detecting Tf, Td and Pg was associated with sites≥6 (OR=1.9, 2.6 and 2.4, respectively). The risk of being positive for Tf and Pi was significantly decreased in smokers (OR=0.3 and 0.3, respectively)																						.VD prevalence significantly increases with age. .VD is predicted from the variables: smoking, age, number of teeth, PI, GI, PPD, sex. .The OR associated with narghile-use and cigarette smoking was statistically significant (OR = 3.4 [1.9-6.1][b], OR=3.9 [2-5.6][b])	

BL: bone loss. **PBH:** periodontal-bone-height. **PM:** periodontal-microflora : **Aa:** *A. actinomycetemcomitans*; **Cr:** *C. rectus*; **Ec.** *E. corrodens*; **Fn:** *F. nucleatum*; **Pg:** *P.gingivalis*; **Pi:** *P. intermedia*; **Pn:** *P. micros* ; **Pn:** *P.nigrescens* , **Si:** *S.intermedius* , **Sn:** *S. sanis* , **Td:** *T. denticola*; **Tf:** *T. forsythensis*.

For the rest of abbreviation, please see Table 1.

[b]Data are mean [95% confidence interval] and prevalence for BL.

Significant differences: [a]NS vs. CS. [b]NS vs. Non-S. [c]NS vs. MS.

Table 3. Results of studies aiming to evaluate the effects of narghile-use on oral mucosa (clinical studies).

1st author	El-Hakim(45)	Al-Belasy(46)	Daugi(49)	Al-Attas(50)
	Oral-cancer	Dry-socket	Suspicious-lesion	Suspicious-lesion
NS		.26%[b]	.14[b]	.Not-applied
CS		.16%	.NA	. Not-applied
Non-S		.7%	.3	. Not-applied
	.2 cases of squamous cell carcinoma .1 case of keratoacanthoma	.Similar incidences between NS and CS. .Incidence not age dependent. .Compared with Non-S, NS who smoked the day of surgery (35%) or the first day after surgery (24%) had a significantly increased dry-socket incidence.	.Smoking bidi or narghile: statistically significant risk factors among referrals for the suspicious-lesion. .Odds-ratio of NS (4.42 (2.32-8.41)[b]) is the highest, compared to smoking bidi ((3.06 (1.60-5.84)[b]) or chewing tobacco (1.97 (0.97-3.98)[b].	.Higher risk and significant association with suspicious-lesion among tobacco and betel nut chewers.

For abbreviation, please see Table 1.
[b]Data are mean [95% confidence interval] and incidence for dry-socket.
Significant differences: [a]NS vs. CS. [b]NS vs. Non-S. [c]NS vs. MS.

Table 4. Results of studies aiming to evaluate the effects of narghile-use on oral mucosa (histological studies)

1st author	Ali(47)							El-Setouhy(48)		Seifi(51)						Al-Amrolh(52)			
	Ac	Ed	Ie	Ii	Ok	Pk	Arr	TMN	CMN	Buccal-mucosa		Tongue		Mouth-floor		TM	TL	%tail DNA	Fragmented DNA
										N/C	FR	N/C	FR	N/C	FR				
NS	90/0	45/0	54/0	36/9	0/0	54/0	54/9	10±4[a,b] 2-26[c]	8±3[a,b]	0.3± 0.002[a,b]	1.3± 0.02[a,b]	0.35± 0.004[a,b]	1.4± 0.02[a,b]	0.3± 0.008[a,b]	1.2± 0.09[a,b]	186±26[b]	456±71[b]	97±19[b]	32±3.3[b]
CS	100/0	36/0	64/45	64/9	9/0	90/0	100/0	NA		0.4± 0.003[a,b]	1.7± 0.02[a,b]	0.4± 0.001[a,b]	1.8± 0.02[a,b]	0.4± 20.009[a,b]	1.6± 0.04[a,b]				
Non-S	73/0	9/0	54/54	45/9	27/0	54/0	54/0	4±2[a] 1-9[c]	4±2[a]	0.24± 0.001[a,b]	1.1± 0.009[a,b]	0.24± 0.002[a,b]	1.14± 0.02[a,b]	0.24± 0.007[a,b]	1.01± 0.01[a,b]	0.05±0.001[a]	9±1.3[a]	1.12±0.02[a]	3.4±0.05[a]
	.Histopathologic changes in the oral-mucosa of both sides: no significant differences between the 3 groups. .Pathologic changes of the oral-mucosa were related mainly to takhzeen al-qat.							.Mean TMN and CMN significantly higher (> 2 folds) among NS vs. Non-S.		Differences in: .N/C ratio and FR in tongue area, mouth-floor and buccal-mucosa of smokers was statistically significant. .% of inflammation in 3 different areas (buccal-mucosa, tongue and mouth-floor) among CS (90%, 100% and 85%, respectively), NS (70%, 100% and 100%, respectively) and Non-S (45%, 77.5% and 77.5%, respectively) was statistically significant. .% of candida in mouth-floor and buccal-mucosa among CS, NS and Non-S was statistically significant.						.The comet assay parameters (TM, TL, % tail DNA, fragmented DNA) in buccal cells are higher among NS vs. Non-S.			

CMN: cells micronuclei. FR: Feret ratio (maximum to minimum nuclear diameter ratio). N/C: nucleus/cytoplasmic sizes. TL: tail-length. TM: tail moment. TMN: total micronuclei.
Histopathologic changes in the oral-mucosa: Ac: acanthosis; Arr: abnormal rete ridges "elongated"; Ed: epithelial-dysplasia; Ie: intracellular-edema; Ii: inflammatory-infiltration; Ok: orthokeratinization; Pk: parakeratinization.
For the rest of abbreviation, please see Table 1
Data are mean±SD* or range (minimum-maximum)'. For Ali(47), data are percentage: chewing side/contralateral side
Significant differences: [a]NS vs. CS. [b]NS vs. Non-S. [c]CS vs. MS. [d]ANOVA between the 3 groups

Effects on oral-mucosa

Tables 3 and 4 display the effects of narghile-use on oral-mucosa (lips, alveolar ridges, buccal-mucosa, tongue and mouth-floor)(29, 45, 47-52).

Oral-lesions : The evidence on the association of narghile-use and oral-lesions, tested in some studies(47, 49, 50), remains inconclusive(16). In one study(47), subjects who practiced 'takhzeen al-qat' were recruited. This practice is distinct from narghile-use and it consists in chewing a green-leaved plant for its stimulant effects(47). When the three groups (CS, Non-S and NS) were compared with respect to the histopathologic changes in the oral-mucosa of both sides (chewing side/controlateral side), it was found that changes are more evident in the CS group (regarding the chewing side) and slightly different in the NS group (regarding the opposite side)(47) (Table 4). However, these differences were statistically not significant(47). According to Chaouachi (67), the situation would be clear if the male participants in the "qat parties" of Ali study(47), were not also CS. In these conditions, one should remain cautious as far as the causes of histopathologic changes of the oral-mucosa are concerned, because of the confusion factors: simultaneous "qat" and "mada'a" smoking. Another confusion factor could be the inclusion of females only in the NS group(47). On the other hand, no effects were observed in either groups on the non-chewing side(47). This observation supposed that the histopathologic changes in oral-mucosa observed on the chewing side are probably due to "takhzeen-al-qat"(47). In a second study(49), narghile-use was associated with a greater referral rate for oral suspicious-lesions to develop cancer after adjusting various confounders. The most recent study(50) found insignificant association with oral suspicious-lesions. In a systematic review, Akl et al.(29) judged the overall quality of evidence of these studies to be very low.

Oral-cancer: The case-series study(45)reported two cases of squamous cell carcinoma of lip and one case of lip keratoacanthoma associated with different forms of narghile-use. However, there is no evidence of causality (Table 3). Three studies have investigated the genotoxic effect of narghile-smoke on oral-mucosa(48, 51, 52) (Table 4). In the first study of El-Setouhy et al.(48), the total-number-of-micronuclei and the number of cells-containing- micronuclei were higher in the NS group compared to the Non-S one. However, one major limitation noted in this study(48) was the inclusion of a high percentage of NS reporting exposure to agriculture pesticides (53%) since the latter increase the micronuclei frequency in exfoliated oral cells(68, 69). In the second study(52), the comet assay parameters (tail-moment, tail-length, %tail DNA, fragmented DNA) calculated in collected buccal cells were higher among NS compared to Non-S (no statistical analysis was made). In the last study(51), quantitative cytometric alterations in oral-mucosa were observed among the NS. An increase in nuclear-size in NS group compared to the Non-S one was observed. It seems that an increase in nuclear-size is a kind of cell adaptation in response to the oral-mucosa epithelium lesion(51). According to Seifi et al.(51), narghile-use creates a cell irritation which facilitates the aging process of oral mucosal cells. As results, proteins, which are synthesized within the nucleus, divide slowly, which in its turn increase the nuclear-size.

Hypothesis for the association between narghile-use and oral-cancer: A recent study aimed at investigating the relationship between narghile-use and the age of patients when diagnosed with oral-cancer(70). Patients with oral-cancer registered in the Jordanian national cancer registry were asked about frequency of cigarette (66%), narghile (36%) and alcohol (17%) use(70). Analysis adjusted for sex, cigarette-smoking, and alcohol-drinking found that NS were significantly younger when diagnosed with oral-cancer compared with Non-S(70). It seems that narghile-use is an independent risk factor associated with the development of oral-cancer at a younger age(70). As the first step in the treatment of cancer is the early diagnosis, especially in high-risk individuals(51, 71), it is very important to help NS quit smoking. The following three hypotheses, made by El-Hakim and Uthman(45), may have acted, either separately or synergistically, in the development of the neoplasms of the lips: *i)* Carcinogenic chemicals (polycyclic aromatic hydrocarbons and N-nitrosamine compounds) formed during curing, fermentation and combustion of tobacco, are dissolved in the saliva, absorbed and metabolized in the body, and thus liberate their highly reactive carcinogenic intermediate products(72). *ii)* Mechanical trauma and irritation caused by the bamboo or plastic tubes used in the mouth piece; and *iii)* The heat generated from the smoke, and the possible chronic infections that might be contagious because of the use of the same narghile by several individuals.

Rastam et al.(73) proposed the hypothesis that human normal oral epithelial cells are susceptible to narghile-use which enhances the progression of human oral-cancers. Narghile-smoke has been in vitro associated with genotoxicity and cellular changes that may lead to cancer(16). Despite the clear evidence that the mainstream smoke of narghile contains a wide range of carcinogens, the contribution of narghile-use to carcinogenesis is not well established. Up to now, no clinical trial has evaluated the association of narghile-use and oral-cancer. According to Chaouachi and Sajid(74), the medical hypothesis that the mainstream smoke from narghile causes oral-cancer is certainly acceptable. However, more studies with rigorous methodology (simultaneous use of other products, strongly neglected hygiene, unclear current profile and past smoking career) are needed.

CONCLUSION

To summarize, this review outlined the effects of narghile-use on oral health. There is a high risk that this form of tobacco may have harmful effects on the oral cavity. The greatest impact demonstrated up to now is on the periodontal health. Extensive well-designed epidemiological studies, in preference longitudinal, are needed to assess the effect of narghile-use on oral tissues.

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SUPPLEMENTARY DATA

Collected data and applied definitions

Clinical data

Plaque-index**(1-3)**: it evaluates the oral hygiene and records both soft debris and mineralized deposits on the teeth**(4)**. The plaque-index criteria are**(4)**: *0:* no plaque; *1:* a film of plaque adhering to the free gingival margin and adjacent area of the tooth, which cannot be seen with the naked eye, but only by using disclosing solution or by using probe; *2:* moderate accumulation of deposits within the gingival pocket, on the gingival margin and/or adjacent tooth surface, which can be seen with the naked eye; and *3:* abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

Gingival-index**(1-3)**: it evaluates the gingival condition and records qualitative changes in the gingiva**(5)**. It scores the marginal and interproximal tissues separately on the basis of zero to three. The gingival-index criteria are**(5)**: *0:* normal gingiva; *1:* mild inflammation (slight change in color and slight edema but no bleeding on probing); *2:* moderate inflammation (redness, edema and glazing, bleeding on probing); and *3:* severe inflammation (marked redness and edema, ulceration with tendency to spontaneous bleeding).

Plaque%**(2)**: is the frequency of surfaces with a plaque score of one or more**(2)**.

Gingival-bleeding**(1, 2)**: is the frequency of gingival sites denoting gingival-bleeding on probing**(2)**.

Probing-pocket-depth**(1, 3, 6)**: is the distance in mm from the margin of the free gingival to the base of the sulcus**(1)**.

Clinical-attachment-loss**(1)**: is the distance from the cementoenamel junction to the base of the sulcus**(1)**.

Periodontal-disease**(1, 3)**: arbitrary defined as the occurrence of ten or more sites with a probing depth of five mm or more per individual**(3)**.

Dry-socket**(7)**: is a disruption of the healing process in an extraction site after clot formation but before wound organization**(8)**.

Suspicious-lesions**(9, 10)**: is a lesion developed in the oral-mucosa which can be potentially malignant**(9)**. The diagnosis is done following the criteria for the visual-tactile-examination of oral-mucosal lesions**(11)**in one study**(9)** and after an intraoral examination and involve any lesion which is red, painless, firm, indurated and had a history of being unresolved for more than 14 days in another study**(10)**.

Oral-cancer**(12)**: is a malignant lesion that occurs at various levels of the oral cavity (lip, tongue and mouth)**(13)**. The diagnosis is obtained after a biopsy**(12)**.

Radiological data

Periodontal-bone-height**(14)**: is the distance from the apex to a point where lamina dura became continuous with the compact bone or the most apical point of the defect**(14)**.

Bone-loss**(14)**: arbitrary defined as a bone height level 70% or less**(14)**.

Vertical-bone-defect**(15)**: is a one-sided bone resorption of the interdental marginal bone ≥ two mm that had a typical angulation towards either the mesial or distal aspect of the root**(15)**. The prevalence of vertical-bone-defect is estimated from the number of individuals exhibiting one or more vertical-bone-defect**(15)**. Severity of vertical-bone-defect**(15)** was arbitrary defined as the frequency of sites with a vertical-bone-defect in relation to the frequency of sites measured in the individual, and expressed as proportion per person**(15)**.

Two different techniques have evaluated the peridontium radiologically: panoramic radiography evaluating the Periodontal-bone-height**(14)**, full set intraoral radiographs including 16 periapical and four bitewings projection for each individual**(15)**. These two techniques are the most commonly used to diagnose the bone-loss because of its low cost, convenience, and high resolution**(16)**. However, while evaluating the images, with conventional 2D image is hard to identify a 3D structure**(16)**.

Biological data

Periodontal-microflora**(6)**: it consists of microorganisms that colonize the periodontal pocket**(6)**. The periodontal-microflora investigation was lead using the checkerboard DNA-DNA hybridization**(17)**.

Tail-moment**(18)**: is the product of the tail-length and the fraction of total DNA in the tail. Tail-moment incorporates a measure of both the smallest detectable size of migrating DNA (reflected in the comet tail-length) and the number of relaxed/broken pieces (represented by the intensity of DNA in the tail)**(19).**

Tail-length**(18)**: is the distance of DNA migration from the body of the nuclear core and it is used to evaluate the extent of DNA damage**(19)**.

%Tail DNA**(18)**: 100 - [Head optimal intensity/(Head optimal intensity + Tail optimal intensity)] x 100**(19)**.

Fragmented DNA**(18)**: is a DNA which the strands are separated or broken into pieces.

Nuclear-size**(20)**: is the size of the nucleus in each cell**(20)**.

Cytoplasmic-size**(20)**: is the size of the cytoplasm in each cell**(20)**.

Nuclear/Cytoplasmic ratio**(20)**: is the ratio between nuclear-size and cytoplasmic-size. Its increase is one of the main symptoms of premalignant and malignant lesions**(20)**.

Feret-ratio**(20)**: big diameter of the nucleus/small diameter of the nucleus ratio**(20)**.

Micronuclei**(21)**: is a small intranuclear DNA structure in exfoliated human oral cells separated from the main nucleus of the basal epithelial layers**(22)**.

Total-number-of-micronuclei**(21)**: is the total number of micronuclei per 1000 cells per subject**(21)**.

Number-of-cells-containing- micronuclei**(21)**: is the number of cells containing Micronuclei per 1000 cells per subject**(21)**.

The Micronuclei test, one of the most rapid and efficient techniques to study the genetic stability in human cells**(23)**, was used for early identification of the carcinogenic process**(21).** The Micronuclei are produced during early events in human carcinogenic processes especially in the oral cavity**(8, 24)**.

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