Update of Intra and Extra Oral Causes of Halitosis: A Systematic Review

Mariona Monfort-Codinach[1], Eduardo Chimenos-Küstner[2], Rui Alburquerque[3], José López-López[2]

[1]DDS. Dentist, Postgraduate in Oral Medicine, School of Denstistry, Univesity of Barcelona, Spain. [2]MD, DDS, PhD. Doctor Specialist in Stomatology, Professor of Oral Medicine, School of Dentistry, University of Barcelona, Spain. [3]DDS, MS, PhD. Academic clinical lecturer in Oral Medicine. School of Dentistry. University of Birmingham, United Kingdom.

Abstract

Aim: To systematically review the different causes of halitosis, both intra oral and extra oral.

Methods: PubMed-MEDLINE was searched to identify potential relevant studies. The keywords used to search were "halitosis", "bad-breath" and "oral malodour causes". The inclusion criteria involved articles published between 2009 and 2014, written in or translated to English which included reviews, cross-sectional studies, randomised clinical trials, non randomised trials, prospective observational studies and case-control studies.

Results: From the 465 studies initially selected, when the inclusion criteria was applied and reviewed by the authors, 39 articles provided relevant information about the aetiology of halitosis. This included 11 reviews, 12 cross-sectional studies, 7 randomised and 2 non randomised trials, 2 prospective observational studies and 5 case-control studies.

Conclusion: Halitosis has a complex aetiology, although majority of the studies agree that in 90% of cases, it is linked to an intra oral cause, specifically when Volatile Sulphur Compounds (VSC) are produced by bacterial decomposition. Coating of the tongue and periodontal disease are the main aetiological factors. More research has to be done to clarify the exact pathophysiological mechanism of halitosis.

Key Words: Halitosis, Causes, Diagnosis, Oral, Detection

Introduction

Halitosis can also be referred to by other terms such as bad breath, oral malodour, foetor oris [2], fetid halitus or stinking mouth [1]. All these terms define an unpleasant or offensive odour, emanating from the oral cavity, for both the affected individual and those with whom they interact. This condition may be caused by a number of factors, including intra or extra oral sources, and may or may not be a linked to a pathological condition [2].

Non-pathological causes that may contribute to halitosis include the consumption of certain products (drugs/ foods), alcohol consumption and tobacco [3-5]. Oral malodour is one of the major complaints made by patients visiting the dentist, ranking only behind dental caries and periodontal disease [2,4]. Precise estimates of the prevalence of halitosis are not possible to obtain [5]. Some studies have estimated the prevalence of halitosis to be between 22% and 50%, others between 6% and 23% [6]. According to the American Dental Association, Settineri et al. [6] report that 50% of the adult population have suffered from an occasional oral malodour disorder, while 25% appear to have a chronic problem.

Numerous detections systems are available for measuring halitosis but the "gold standard" is still the organoleptic measurements [7]. The scoring system is based on a numerical scale of 1 to 5. A score of 1 relates to barely noticeable odour while a score of 5 corresponds to extremely foul odour [7]. The human nose is capable of smelling and defining pleasant/ unpleasant and also other organic compounds that come from exhalation, not only the Volatile Sulphur Compounds (VSC) which are considered to be the main reason of oral malodour [2,4,5,8-20]. However, this is an extremely subjective test, with lack of quantification and no reproducibility [10]. Gas Chromatography (GC) analysis can be performed on breath, saliva and tongue debris and almost all components can be detected with high sensitivity and specificity [7,10]. The Halimeter® is an electronic portable gas analysis that calculates the total amount of VSC's, with fast results. It is also portable and reproducible [7,10]. Although there are some limitations, such as the variable cut-off points for the diagnosis of halitosis, a diamine oxidase enzyme, coupled to an electrochemical biosensor to detect biogenic amines in saliva has been developed [21].

According to classification of halitosis by Yaegaki et al. [22] genuine halitosis is defined as obvious malodour with intensity, beyond a socially acceptable level. Pseudohalitosis is defined as obvious malodour not perceived by others, although the patient stubbornly complains of its existence [7,23] it is unusual that patients can detect their halitosis. Some researchers indicate that pseudohalitosis patients have a strong tendency for depression; it is related to somatic and emotional status and associated with psychological disorders [23]. Other studies classify according to psychological aspects in pseudohalitosis, halitophobia and olfactory reference syndrome [10].

Some studies from the halitosis clinic at the University of Basel in Berlin, have shown 12% to 27% of patients presented with psychogenic halitosis [11]. Genuine halitosis is subclassified as physiological or pathological halitosis, and pathological halitosis is subdivided further into oral or non-oral pathological halitosis [7,16,22]. Healthy subjects can have morning breath or physiological halitosis resulting from hyposalivation and proliferation of bacteria, but this

Corresponding author: Dr. José López L, Facultat d'Odontologia.Campus Universitari de Bellvitge. C/ Feixa Llarga s/n. 08907-L'Hospitalet de Llobregat. Barcelona (Spain). Tel: +34 6506457362; Fax: +34 93 3859346; e- mail: jl.lopez@gmail.com

should disappear after a meal [12]. It is also considered as physiological halitosis when the cause is atributed to poor oral hygiene [20,22]. Halitosis has been classified as primary or secondary [20]. Primary halitosis refers to respiration exhaled by the lungs, whereas secondary halitosis originates either in the mouth or upper airways [13,20]. It is believed that 85-90% of the cases of halitosis have an intra oral origin [1-3,5-8,10,12,19,24-26], specifically due to bacterial decomposition of organic material [10,14,25], mainly through the coating of the tongue/periodontal disease [5,7-10,12,15,18,21,27-30]. The oral microflora, chiefly gram-negative anaerobic bacteria, metabolise largely sulphur-containing aminoacids like cysteine or methionine that are found in the saliva, gingival crevicular fluid and in debris coating the tongue, into VSC such as hydrogen sulphide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulphide ($(CH_3)_2S$) [8,17,31].

Aim

The aim of this systematic review is to synthesise the potential causes for halitosis, in order to help identify the knowledge gaps concerning this topic. The conclusions drawn from this review will suggest areas for future research.

Methods

A systematic review to unify and summarise all the published literature about halitosis has been performed. An electronic search of MEDLINE (pubmed) was used to identify potentially relevant study databases. The words that were searched included “halitosis”, “bad breath” or “oral malodour causes”. Only articles written/ translated to English were included. The inclusion criterias also included articles published in English in the last 5 years (2009 to July 2014) which were : reviews, cross-sectional studies, randomised clinical trials or non randomised trials, prospective observational studies and case-control studies. All titles and abstracts were independently reviewed by the authors (AMC, EDC, RA, JLL) for inclusion. If the abstract provided insufficient information, strong bias or if the reviewers disagreed, the authors independently reviewed the full text before reaching consensus through discussion.

Results

The first search had showed 1487 items although when restricting to the last five years, the total figure reduced to 465 studies. When applying the inclusion criteria and the review process previously described, 39 articles provided relevant information about the aetiology of halitosis: including 11 reviews, 12 cross-sectional studies, 7 randomised and 2 non randomised trials, 2 prospective observational studies and 5 case-control studies (*Table 1*).

Prospective studies

'The prospective studies [1,34] analyzed a total of 413 patients.Tas et al. [1] studies the relation between halitosis and gastrointestinal pathology while Zurfluh et al. [34] analyses the association of halitosis in patients with orthodontic appliances.

Cross sectional studies

The cross-sectional studies [2-4,6,8,11,16,19,23,28,29,40], showed several intra and extra oral causes for halitosis.

Revision studies

From the review studies [5,7,9,10,20,25,31-33,35,37] we have noticed that none are systematic. These describe diagnostic and pathogenetic factors halithosis as well as its relation to the quality of life of patients. Zalesca et al. [25] provides an overall figure of up to 20% of extra oral casuses such as possible depression.

Randomised control trials

The Randomised clinical trials provided some information about etiology however majority was to identify potential treatments for halitosis.

Non Randomised control trials

From the non randomised clincal trials several causes are identifies such as high urea levels, low salivary flow rates and periodontal disease [24,26]. Liu et al. [26] studies the use of a vaccine using ultraviolet-inactivated Fusobacterium nucleatum in induced periodontal abcess in mice.

Case control studies

Multiple causes for the development of halitosis are identified such as radiotherapy [14], gastrointestinal ethiology [27,36] (such as Helicobacter pylori [6], periodiontal disease [39] and the possible effect of the menstrual cycle [38,39]. Kawamoto et al. [39] showed Prevotella intermedia in subjects with periodontitis were significantly higher in the ovulation phase than in the follicular phase.

Discussion

Recently, halitosis has received much more scientific attention. The exact pathophysiological mechanism of halitosis is unclear, but all studies now agree 85-90% of cases are of intra oral origin [1-3,5-8,10,12,19,24,25,31-33]: tongue coating and periodontal disease are the main causes [5,7-10,12,15,18,21,27-30] and VSC are the major compounds that contribute to oral malodour [2,4,5,7-20,33]. Nevertheless, probably due to the numerous factors that can influence a systemic cause, there is much more controversy regarding the nature of systemic origin. Most of the studies declare that extra oral causes are predominantly found in the ear, nose and throat regions or in rare cases in the gastrointestinal tract [1,5,11,16], but metabolic disorders like diabetes, liver pathology, endocrinological diseases, medications, mouth breathing or stressful situations have been studied as causes or possible contributions that increase halitosis [1-3,5,9,10,24,32]. One of the limitations of this review is that the search methodology used in this article cannot guarantee that all articles pertinent to the topic were included. This is because other databases may also include information in the field of halitosis.

Further research considering other languages than the ones mentioned and other databases should be carried out. Subjects with intra oral halitosis had odour stemming from the oral cavity but not the nose, whereas subjects with extra oral halitosis had blood-borne odour that was measurable from both the mouth and the nose. Dimethyl sulphide was the only malodourous compound found in significant levels for extra oral halitosis, whereas methyl mercaptan and hydrogen sulphide were compounds most associated with intra oral halitosis [7]. A summary of intra oral and extra oral causes is shown in *Table 2*.

Oral malodour originates mainly from the mouth itself while the malodourous substrates are most commonly associated with microbial metabolism. The oral surfaces are colonized by large number of bacterial species which are known to produce malodourous compounds. However, no obvious association exists between halitosis and any specific bacterial infection, suggesting that bad breath reflects complex interactions between several oral bacterial species [19]. Most of the major malodourous compounds are Volatile Sulphur Compounds (VSCs) such as hydrogen sulphide (H_2S), methylmercaptan (CH_3SH) and dimethyl sulphide ($(CH_3)_2S$) [5,10,15,16,19]. In vitro and in vivo studies have demonstrated that oral gram negative anaerobic bacteria such as Porphyromonas Gingivalis (P.G.), Fusobacterium Nucleatum (F.N.), Treponema Denticola (T.D.) and several species of other oral bacteria can produce VSCs [7,31,33]. These bacteria can be isolated from the subgingival plaque in gingivitis or periodontitis patients, and from the saliva and

Table 1. *Differents studies acoding to type, to author, location , sample size and findings/etiology.*

Type of Study	Author	Year	Location	Sample Size (N)	Findings/Etiology of Halitosis
Prospective study	Tas A et al. [1]	2011	Turkey	N=358	Extra oral: Gastrointestinal cause (regurgitation, bloating and nausea)
	Zurfluh MA et al. [34]	2013	Switzerland	N=55	Intra oral: Fixed orthodontic appliance
Cross-sectional studies	Al-Zahrani MS et al. [2]	2011	Saudi Arabia	N=38	Extra oral : Diabetes
	Motta LJ et al. [3]	2011	Brazil	N=55	Intra-oral: mouth-breathing
	Takeshita T et al. [4]	2010	Japan	N=240	Intra-oral: Periodontal disease, tongue coating (higher concentration of Streptococcus, Granulicatella, Rothia, and Treponema species)
	Settineri S et al. [6]	2010	Italy	N=1052	Extra oral: anxiety, alcohol consumption, urinary system pathologies Intra oral: gum diseases, poor oral hygiene
	Tangerman A, Winkel EG [8]	2007	Netherland	N=58	Extra oral: Presence of elevated levels of dimethyl sulphide (CH(3)SCH(3)) in mouth and nose breath. Intra oral: CH(3)SH is the main contributor to intra-oral halitosis
	Zürcher A, Filippi A [11]	2012	German	N=465	Extra oral: gastrointestinal causes, ear and nose pathologies. Intra oral: periodontitis, gingivitis, in rare cases, thrush, dental caries, unclean dentures, insufficient dental restorations or poor oral hygiene
	Fukui M et al. [19]	2010	Japan	N=74	Intra oral: High concentration of cortisol
					Salivary cortisol reflects a status of chronic stress condition, psychosomatic halitosis might be closely related to this state of chronic stress
	Suzuki N et al. [16]	2008	Japan	N=326	Intra oral: Periodontal disease and tongue coating
	Zaitsu T et al. [22]	2011	Japan	N=262	Extra oral: Anxiety
	Struch F et al. [28]	2008	German	N=417	Extra oral: Gastro esophageal reflux disease Intra oral: Denture-wearing
	Migliario M & Rimondini L [29]	2011	Italy	N=192	Intra oral: Tongue coating and periodontal disease
	De Luca-Monasterios F et al. [40]	2014	Spain	N=98	Intra oral: xerostomia The use of chewing gum as an adjunct in cases of halitosis decreases the VSC.
Reviews	Bollen CML, Beikler t [37]	2012	United States of America	No sample size.	None of them are systematic reviews and in general describe the intra and extra oral causes for halitosis, methods of diagnosis and treatment.
	Aylikci BU et al. 2013 [33]	2013	Turkey		
	Harvey-Woodworth CN [31]	2013	UK		
	Tseng WS [32]	2014	China		
	Rösing CK, Loesche W [5]	2011	Brazil		
	Armstrong BL et al. [7]	2010	United States of America		
	Bollen CM, Beikler T [10]	2012	German		
	Cortelli JR et al. [9]	2008	Brazil		
	Scully C & Greenman [20]	2012	United Kingdom		
	Zolesca A et al. [25]	2012	Poland		
	Tangerman A [35]	2002	Netherland		

Randomised clinical trials	Tolentino Ede S et al. [12]	2011	Brazil	N=50	Intra oral causes: saliva and tongue coating pH The aim of this work was to evaluate saliva and tongue coating pH in patients with a healthy mouth with morning bad breath before and after use of different oral mouth rinses. The enzymatic solution decreased saliva and tongue coating pH immediately after rising.
	Brunner F et al. [13]	2010	Switzerland	N=100	Study to evaluate the best method for measuring oral malodor in which the Halimeter correlated best with the organoleptic assessment of halitosis
	Shinada K et al. [15]	2010	Japan	N=15	Intra oral causes: plaque, tongue coating accumulation and the counts of *Fusobacterium nucleatum* in saliva EL ClO2 (chlorine dioxide) helps in reducing plaque, tongue coating accumulation and the counts of *Fusobacterium nucleatum* in saliva.
	Peruzzo DC et al. [17]	2008	Brazil	N=50	The use of a flavor-containing dentifrice helps in preventing VSCs formation in morning bad breath.
	Kurata H et al. [18]	2008	Japan	N=35	Intra oral: Periodontal pathogens (*Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, Prevotella intermedia* and *Prevotella nigrescens*)
	Dadamio J et al. [21]	2011	Belgium	N=50	The new enzymatic test (biogenic amines as bio-markers of oral malodor), interpreted by means of a simple color scale, has the potential to be used as an adjunct chair-side test for oral malodor diagnosis.
	Takeuchi H et al. [29]	2010	Japan	N=192.	Intra oral: tongue coating and periodontal disease
Non Randomised clinical trials	Keles M et al. [24]	2011	Turkey	N=42	Extra oral: Renal disease High blood urea nitrogen levels and low salivary flow rates were found to be associated with halitosis..
	Liu PF et al. [26]	2009	United States of America	Laboratory: Mouse models for investigating chronic halitosis	Intra oral: Periodontal disease In vitro study on induced periodontal pockets mouse model to evaluate the effectiveness of a vaccine using a novel ultraviolet-inactivated *Fusobacterium nucleatum*, a representative oral bacterium for halitosis. The study shows the vaccine provides an alternative option to conventional antibiotic treatments for chronic halitosis associated with abscesses.
Case-control studies	Albuquerque DF et al. [14]	2010	Brazil	N=35	Extra oral: Radiotherapy Intra oral: Hyposalivation and poor oral health
	Kingber S et al. [27]	2010	Israel	N=94	Extra oral: General gastrointestinal pathology
	Yilmaz AE et al. [36]	2012	Turkey	N=53	Extra oral: Helicobacter pylori
	Lima PO et al. [38]	2013	Brazil	N=14	Extra oral: VSC was higher in the menstrual and premenstrual phases when compared with men and the follicular phase
	Kawamoto A et al. [39]	2010	Japan	N=22	Intra oral: Periodontal disease (The number, and salivary levels, of *Prevotella intermedia* in subjects with periodontitis were significantly higher in the ovulation phase than in the follicular phase.)

the dorsum of the tongue in healthy subjects [5,10,15,19]. Odour outcomes are significantly correlated with total counts of bacteria and the diversity of each type [7,15]. Several microorganisms recovered from periodontal lesions of gingivitis and periodontitis can produce large amounts of VSCs. The bacterial interactions are most likely to occur in the gingival crevices and periodontal pockets, but oral malodour can also arise from the posterior dorsal surface of the tongue. A consequence of its large and irregular surface is that it is an ideal niche for oral bacteria. Since desquamating epithelial cells and remnants are available, putrefaction occurs [5,10,12,14,15,18,27,28]. During the process of bacterial putrefaction, however, compounds other than sulphur compounds are also formed. Peptides are hydrolysed to aminoacids which can be metabolized further to amines or polyamines. Even when the contribution of all of these compounds to oral malodour has not been found, other studies have clearly demonstrated a significant correlation between some of them and oral malodour [21]. The researchers concluded that halitosis is a result of multifaceted interactions between diverse species of bacteria [7]. Other oral pathological sources that have been suggested as a cause of halitosis are dental cavities, exposed tooth pulps, healing wounds, interdental food impaction, dentures kept in at night or not regularly cleaned, fixed orthodontic appliances, restorative crowns that are not well adapted, cysts with fistula draining into the mouth, peri-implantitis, pericoronitis, oral cancer, ulcerations and factors causing a decreased salivary flow rate [1,2,16,24,34]. Saliva plays a central role in the development of bad breath. Patients with xerostomia have an increase level of plaque on their teeth and tongue, the antimicrobial activity of the saliva disappears and there is a transition from gram-positive to gram-negative species [3,10]. There are a number of clinical conditions that can cause changes to salivary

Table 2. *Causes of halitosis.*

INTRA ORAL ORIGINS (85-90%)	**EXTRA ORAL CAUSES (10%)**
Poor oral hygiene	Ear, nose and throat regions
Tongue coating	Acute tonsillitis
Periodontal disease	-Postnasal drip
Dental cavities	-Cleft palate
Exposed tooth pulp	- Atrophic rhinitis
Healing wounds	-Sinusitis
Interdental food impactation	Gastrointestinal tract
Dentures not cleaned	-Gastroesophageal reflux disease
Cyst with fistula	-H. Pylori
Periimplantitis	-Peptic ulcer disease
Pericoronaritis	-Zenker's diverticulum
Oral cancer	Bloodborne halitosis
Low salicary flow rate	- Metabolic disorder (ej: diabetes)
	- Liver pathology
	-Renal failure
	- diseases
	-Medication
	Mouth breath
	Stressfull
	Menstrual cycle

patterns. One such condition is a change from nasal to mouth breathing, which causes adaptive changes drying the mucosa [3]. Albuquerque et al. [14] evaluated halitosis and sialometry in patients submitted to head and neck radiotherapy, because of the radiosensitivity, the salivary glands had a decreased potential of saliva production. The results showed a strong association between hyposalivation and halitosis. This study and the many causes of xerostomia, show it is important to find out and eliminate the cause of hyposalivation in the treatment of halitosis.

Several extra-oral causes have been suggested and studied. Extra oral halitosis can be subdivided into: halitosis from the Ear, Nose and Throat region (ENT), pulmonary pathology, gastrointestinal tract and blood-borne halitosis. In blood-borne halitosis, malodourant compounds in the bloodstream are carried to the lungs where they volatilize and enter the breath. Potential source of blood-borne halitosis are: some systemic diseases, e.g. liver pathology and endocrinological diseases, metabolic disorders, medications and certain foods [7,31,35].

Acute tonsillitis is the most important cause of halitosis from the ENT region.. Bronchiectasis, lung abscesses or necrotizing lung neoplasia may cause an unpleasant odour [1,5,10,32,33]. Most of the studies mention several digestive diseases like gastroesophageal reflux or Helicobacter pylori that are associated with halitosis. In Gastro-Oesophogeal Reflux Disease (GORD), oesophageal mucosa can break down and these areas can be inhabited by bacteria, producing VSCs. This could explain a strong association between the occurrence of halitosis and regurgitation as a symptom [1,27]. Some studies reported that Helicobacter pylori is able to produce VSCs, confirming the existence of it in the oral cavity and an improvement of halitosis after eradication treatment for H. pylori [36]. But more research needs to be done to clarify a clear correlation between H. pylori and halitosis. Zenker's diverticulum and bleeding of the oesophagus is also related to unpleasant odour. In cases of intestinal obstruction, a faecal mouth odour may be detectable [10]. Several well-documented aetiologies for non-oral malodour include renal failure, cirrhosis of the liver and diabetes. Chronic renal failure is associated with high Blood Urea Nitrogen (BUN) levels and low salivary output. Peritoneal dialysis plays an important role in decreasing the level of halitosis in end-stage renal disease [10,24]. Diabetic ketoacidosis leads to a typical breath odour. Recent studies showed a significant difference in the mean levels of glycated hemoglobin in subjects reporting and not reporting halitosis, but further studies are needed to explain the nature of this association [2,10]. Trimethylaminuria is a disorder in which the volatile, fish-smelling compound, trimethylamine accumulates and is excreted in the urine, but it is also found in the sweat and breath. The liver can also be involved in oral malodour due to elimination of waste products through the lungs when liver function is reduced, causing the "foetor hepaticus" [10,31].

Other extra oral causes have been suggested that may contribute to increase halitosis e.g. stress or menstrual cycle [5,37,38]. Sex hormones have been suggested to be important modifying factors that may influence the pathogenesis of periodontal disease. One study proved that during the ovulation phase, VSC levels and bleeding on probing were significantly higher in subjects with periodontitis but not in healthy subjects, and the VSC levels in subjects with periodontitis increased in the ovulation phase compared with the follicular phase [39]. Nevertheless, Lima et al. proved that stress increase VSCs production and that these effects are influenced by gender [32]. Apart from medication [37] resulting in a dry mouth, the use of bisphosphonates can also contribute to oral malodour. This can cause jawbone necrosis, a clear origin for an unpleasent odour. Some foods, such as onions or garlic, are also associated with halitosis [37].

Several studies [5,13,20,40] reflect the importance of carrying out the appropriate measures under the right conditions in order to have the most reliable results. It would be difficult to ascertain which factors produced the strongest evidence of halitosis as it would entail a control to avoid contamination from other external sources some of which may

have been consumed some time ago which may obscure the results, such as the use of healthcare products, consumption of alcohol, tobacco and food.

Conclusions

In conclusion, all the studies agree that around 90% of halitosis is linked to an intra oral cause, with tongue coating, periodontal disease and insufficient oral hygiene being the main culprits. Most major malodourous compounds are VSCs produced by oral gram negative anaerobic bacteria. There is also agreement that around 10% of halitosis is created through extra oral causes, but more research has to be done to clarify its exact pathophysiological mechanism.

Conflict of Interest

The authors declare that they have no conflict of interests.

References

1. Tas A, Köklü S, Yüksel I, Basar O, Akbal E, Cimbek A. No significant association between halitosis and upper gastrointestinal endoscopic findings: a prospective study. *Chinese Medical Journal*. 2011; **124**: 3707-3710.

2. Al-Zahrani MS, Zawawi KH, Austah ON, Al-Ghamdi HS. Self reported halitosis in relation to glycated hemoglobin level in diabetic patients. *The Open Dentistry Journal*. 2011; **5**: 154-157.

3. Motta LJ, Bachiega JC, Guedes CC, Laranja LT, Bussadori SK. Association between halitosis and mouth breathing in children. *Clinics* (Sao Paulo). 2011; **66**: 939-942.

4. Takeshita T, Suzuki N, Nakano Y, Shimazaki Y, Yoneda M, Hirofuji T. Relationship between oral malodor and the global composition of indigenous bacterial populations in saliva. *Applied and Environmental Microbiology*. 2010; **76**: 2806-2814.

5. Rösing CK, Loesche W. Halitosis: An overview of epidemiology, etiology and clinical management. *Brazilian Oral Research*. 2011; **25**: 466-471.

6. Settineri S, Mento C, Gugliotta SC, Saitta A, Terranova A, Trimarchi G. Self-reported halitosis and emotional state: Impact on oral conditions and treatments. *Health and Quality of Life Outcomes*. 2010; **8**: 34.

7. Armstrong BL, Sensat ML, Stoltenberg JL. Halitosis: A review of current literature. *Journal of Dental Hygiene*. 2010; **84**: 65-74.

8. Tangerman A , Winkel EG. Intra- and extra-oral halitosis: Finding of a new form of extra-oral blood-borne halitosis caused by dimethyl sulphide. *Journal of Clinical Periodontology*. 2007; **34**: 748-755.

9. Cortelli JR, Barbosa MD, Westphal MA. Halitosis: A review of associated factors and therapeutic approach. *Brazilian Oral Research*. 2008; **22**: 44-54.

10. Bollen CM, Beikler T. Halitosis: The multidisciplinary approach. *International Journal of Oral Sciences*. 2012; **4**: 55–63.

11. Zürcher A, Filippi A. Findings, diagnoses and results of a halitosis clinic over a seven year period. *Schweiz Monatsschr Zahnmed*. 2012; **122**: 205-216.

12. Tolentino Ede S, Chinellato LE, Tarzia O. Saliva and tongue coating pH before and after use of mouthwashes and relationship with parameters of halitosis. *Journal of Applied Oral Science*. 2011; **19**: 90-94.

13. Brunner F, Kurmann M, Filippi A. The correlation of organoleptic and instrumental halitosis measurements. *Schweiz Monatsschr Zahnmed*. 2010; **120**: 402-408.

14. Albuquerque DF, de Souza Tolentino ES, Amado FM, Arakawa C , Chinellato LE. Evaluation of halitosis and sialometry in patients submitted to head and neck radiotherapy. *Medicina Oral, Patología Oral y Cirugía Bucal*. 2010; **15**: 850-854.

15. Shinada K, Ueno M, Konishi C, Takehara S, Yokoyama S, Zaitsu T. Effects of a mouthwash with chlorine dioxide on oral malodor and salivary bacteria: A randomized placebo-controlled 7-day trial. *Trials*. 2010; 12: 11-14.

16. Suzuki N, Yoneda M, Naito T, Iwamoto T, Masuo Y, Yamada K. Detection of helicobacter pylori DNA in the saliva of patients complaining of halitosis. *Journal of Medical Microbiology*. 2008; **57:** 1553-1559.

17. Peruzzo DC, Salvador SL, Sallum AW, Nogueira-Filho Gda R. Flavoring agents present in a dentifrice can modify Volatile Sulphur Compounds (VSCs) formation in morning bad breath. *Brazilian Oral Research*. 2008; **22**: 252-257.

18. Kurata H, Awano S, Yoshida A, Ansai T, Takehara T. The prevalence of periodontopathogenic bacteria in saliva is linked to periodontal health status and oral malodour. *Journal of Medical Microbiology*. 2008; **57**: 636–642.

19. Fukui M, Hinode D, Yokoyama M, Yoshioka M, Kataoka K, Ito HO. Levels of salivary stress markers in patients with anxiety about halitosis. *Archives of Oral Biology*. 2010; **55**: 842-847.

20. Scully C, Greenman J. Halitology (breath odour: Aetiopathogenesis and management). *Oral Diseases*. 2012; **18**: 333-345.

21. Dadamio J, Van Tornout M, Van den Velde S, Federico R, Dekeyser C, Quirynen M. A novel and visual test for oral malodour: First observations. *Journal of Breath Research*. 2011; **5**: 046003.

22. Yaegaki K, Coil JM. Examination, classification, and treatment of halitosis; Clinical perspectives. *Journal of Canadian Dental Association*. 2000; **66**: 257-261.

23. Zaitsu T, Ueno M, Shinada K, Wright FA, Kawaguchi Y. Social anxiety disorder in genuine halitosis patients. *Health Quality Life Outcomes*. 2011; **3**: 94.

24. Keles M, Tozoglu U, Uyanik A, Eltas A, Bayindir YZ, Cetinkaya R. Does peritoneal dialysis affect halitosis in patients with end-stage renal disease? *Peritoneal Dialysis International*. 2011; **31**: 168-172.

25. Zalewska A, Zatoński M, Jabłonka-Strom A, Paradowska A, Kawala B, Litwin A. Halitosis: A common medical and social problem. A review on pathology, diagnosis and treatment. *Acta Gastro-Enterologica Belgica*. 2012; **75**: 300-309.

26. Liu PF, Haake SK, Gallo RL, Huang CM. A novel vaccine targeting fusobacterium nucleatum against abscesses and halitosis. *Vaccine*. 2009; **27**: 1589-1595.

27. Kingber S, Stein M, Zion N, Shaoul R. The gastrointestinal aspects of halitosis. *Canadian Journal of Gastroenterology*. 2010; **24**: 552-556.

28. Struch F, Schwahn C, Wallaschofski H, Grabe HJ, Völzke H, Lerch MM. Self-reported halitosis and gastro-esophageal reflux disease in the general population. *Journal of General Internal Medicine*. 2008; **23**: 260-266.

29. Migliario M, Rimondini L. Oral and non oral diseases and conditions associated with bad breath. *Minerva Stomatologica*. 2011; **60**: 105-115.

30. Takeuchi H, Machigashira M, Yamashita D, Kozono S, Nakajima Y, Miyamoto M. The association of periodontal disease with oral malodour in a Japanese population. *Oral Diseases*. 2010; **16**: 702-706.

31. Harvey-Woodworth CN. Dimethylsulphidemia: The significance of dimethyl sulphide in extra-oral, blood borne halitosis.

British Dental Journal. 2013; **214**: 20.

32. Tseng WS. Halitosis: Could it be a predictor of stroke? *Medical Hypotheses*. 2014; **82**: 335-337.

33. Aylikci BU, Colak H. Halitosis: From diagnosis to management. *Journal of Natural Science, Biology and Medicine*. 2013; **4**: 14-23.

34. Zurfluh MA, van Waes HJ, Filippi A. The influence of fixed orthodontic appliances on halitosis. *Schweiz Monatsschr Zahmed*. 2013; **123**: 1064-1075.

35. Tangerman A. Halitosis in medicine: A review. *International Dental Journal*. 2002; **52**: 201-206.

36. Yilmaz AE, Bilici M, Tonbul A, Karabel M, Dogan G, Tas T. Paediatric halitosis and helicobacter pylori infection. *Journal of the College of Physicians and Surgeons Pakistan*. 2012; **22**: 27-30.

37. Bollen CML & Beikler T. Halitosis: The multidisciplinary approach. *International Journal of Oral Sciences*. 2012; **4**: 55-63.

38. Influence of gender and stress on the volatile sulfur compounds and stress biomarkers production. *Oral Diseases*. 2013; **19**: 366-373.

39. Kawamoto A, Sugano N , Motohashi M, Matsumoto S, Ito K. Relationship between oral malodor and the menstrual cycle. *Journal of Periodontal Research*. 2010; **45**: 681-687.

40. De Luca-Monasterios F, Chimenos-Küstner E, López-López J. [Effect of chewing gum on halitosis]. *Medicina Clínica*. 2014; **143**: 64-67.