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Journal of Clinical Case Studies
ISSN 2471-4925 | Open Access

CASE REPORT
Volume 3 - Issue 4 | DOI: http://dx.doi.org/10.16966/2471-4925.175

Higher Levels of Exhaled Dimethylcyclopropane in Patients with Small Intestinal Bowel Overgrowth, Periodontitis when Associated with a Medical History of Cancer

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Received: 21 Sep, 2018 | **Accepted:** 01 Oct, 2018 | **Published:** 06 Oct, 2018

Citation: Bruno D, Fanny B, Jeremy P, Mathilde G, Amandine F, et al. (2018) Higher Levels of Exhaled Dimethylcyclopropane in Patients with Small Intestinal Bowel Overgrowth, Periodontitis when Associated with a Medical History of Cancer. J Clin Case Stu 3(4): dx.doi.org/10.16966/2471-4925.175

Abstract

Background: Periodontitis (PO) is associated with an increased risk of cancer. Breath test is routinely used for detection of Small Intestinal Bowel Overgrowth (SIBO). Specific Volatile Organic Compounds (VOC) may firstly enable early non-invasive detection of cancers and secondly be markers of specific bacteria.
Objective: We investigated whether patients with PO and a medical history of cancer exhale specific gases.
Methods: A retrospective epidemiological study was performed based on data from 3, 110 patients with SIBO; including 453 with PO, 208 with a medical history of cancer and 33 with PO+SIBO+cancer. The study retrieved 65 well-documented case reports of patients with PO plus SIBO, including twelve patients who had a medical history of cancer (group 1) and 53 patients who never experienced cancer (group 2). For these 65 patients, VOC were routinely detected by SPME-GC-SM after 10 to 12 hours of fasting (T_0) and two hours after the intake of sugar (T_2h). Hyaluronic acid (HA) concentration in plasma (which could be a marker of severe chronic inflammation) was also routinely measured. Data on Helicobacter pylori and on Herpes Simplex infection were available.
Results: The ratio dimethylcyclopropane/(Toluene+Phenol+1.3-pentadiene+1-propanol) [DMCP/TPPP] at T_0 enables to differentiate between group 1 and group 2 (0.50 ppm ± 0.26 *versus* 0.28 ± 0.17; p<0.01). The difference between [DMCP/TPPP] at T_0 and at T_2h is also statistically significant (0.15 ppm ± 0.21in group 1 *versus* -0.07 ± 0.20 in group 2; p<0.001). HA was higher in group 1 (78.3 ± 40.5 microg/l *versus* 37.7 ± 19.6; p<0.001).
Conclusion: DMCP/TPPP and HA level may be interesting markers for cancer screening in at risk patients. An implication of Campylobacter species should be further investigated.

Keywords: Dimethylcyclopropane; Hyaluronic; Periodontitis; Cancer

Introduction

Periodontitis (PO) concerns more than 10% of the population [1] and is associated with an increased risk of cancer [2,3]. Chronic inflammation induced by oral or small gut dysbiosis may lead to deleterious interactome and premature death [4,5].

Detection of Small Intestinal Bowel Overgrowth (SIBO) is based on breath test, which should be routinely performed "in the evaluation of common gastroenterology problems" according to a recent consensus [6]. Researchers are ongoing for early non-invasive detection of cancers using exhaled VOC; especially digestive, breast, thyroid and prostatic cancers [7-12].

The pathogenic mechanism of severe inflammation, destruction of tissues associated with PO is unknown. However, the cutting of High-Molecular-Weight-Hyaluronic acid in small fragments of Low-Molecular-Weight-Hyaluronic acid (LMWHA) by bacterial proteases is established in PO [13]. We reported in a preliminary study that the severity of PO is associated with an increased level of plasmatic HA and with an increased risk of adenocarcinoma [14].

LMW-HA is known to increase endothelial permeability, to stimulate receptors of cancer stem cells and to favour cancer cells metastasis [15-18]. Hyaluronidases of oral pathogens may play a role in the occurrence of cancer associated with PO. Since bacteria may

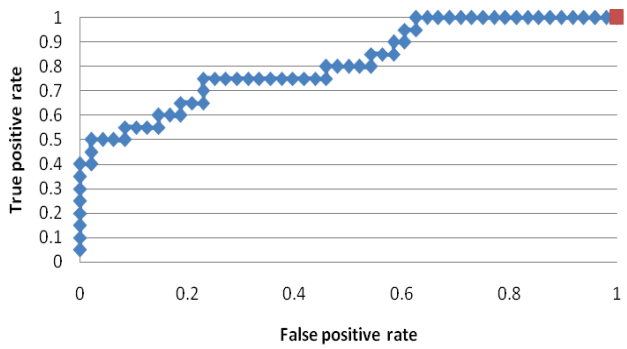

Figure 1: ROC curve for the D/TPPP ratio.

The threshold between group 1 (medical history of cancer) and group 2 (no medical history of cancer) is close to 0. The sensitivity is equal to 75% and the false positive rate is equal to 31.25%. The negative predictive value is equal to 91.7% and the positive predictive value is equal to 96.4%. The values are satisfactory (AUC=0.814), as far as simple screening is concerned.

have a specific gas signature [19], we investigated whether patients with SIBO+PO and severe-associated diseases exhale specific gas. To our knowledge, no similar study has been performed yet.

Material and Methods

All data were collected during the normal course of routine gastroenterological consultations for SIBO.

There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before the work has already been done. This epidemiological retrospective analysis of Case Series cannot therefore be qualify as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria

All patients underwent a breath test and a trans abdominal ultrasound which confirmed SIBO. Patients did not take either antibiotic therapy or any medication which can modify digestive flow for at least 4 months before the breath test.

Patients presented with PO diagnosed by a periodontologist. Patients should have completed an appropriate screening for cancer (colon, stomach, breast, prostate, thyroid) according to the recommendations of the "Institute National du Cancer "(France). Plasmatic hyaluronic acid (HA) dosage had been performed. A full medical history was available, including medication intake. Patients signed a written consent for the epidemiological use of collected data; as all other patients consulting in the gastroenterological clinic.

Exclusion criteria

Ongoing tobacco abuse; lack of hyaluronic acid analysis; lack of breath test or trans abdominal ultrasound; lack of signed consent for epidemiological use of data. Intake of antibiotic therapy or of any medication which may modify digestive flow as well as surgical treatment of periodontitis within the previous 4 months.

Gases analysis

The measurement of VOC implies SPME-GC-MS with collection of gases on a PDMS/CAR, 75 µm (Supelco®) fibres chosen to trap VOCs. The patient breathes in a glass bottle with no plastic part. Condensates remain in the bottom of the bottle whilst the air is evacuated by 8mm glass tube which contains the fibre. Samples were obtained twice after fasting and twice two hours after the intake of sugars (fructose and trehalose). The air of the clinic is permanently Hepa-filtered and UV-decontaminated. Lack of any VOC contamination is checked twice each working-day with two different MX6® devices (Gazdetect® France). SPME-GC-SM analysis was performed within 24 hours. A solid phase micro extraction (SPME) holder with carboxen/polydimethylsiloxane (CAR/PDMS) fibers of 75 µm thickness was purchased from Supelco®. The SPME fiber was inserted into the glass bottle where the patients blew 10 times to collect the sample.

The analysis was performed on a GC-MS instrument (Agilent® GC 7890A/MS 5975C) equipped with a Rxi 624 Sil column (length 60m × inner diameter 250 µm × film thickness 0.25 µm) (Restek®). VOC identification was realized with mass spectra bank. Peak areas corresponding to m/z of each molecule were estimated in Areas Arbitrary Unit (AAU). The values for relative polarity are normalized according to Reichardt C, et al.

Relevant gases were selected according to previous publications on VOC in human breath. Acetonitrile, dichloromethane, ethylacetate, phenylethanol, M-xylene, 2-propanol and P-cymene were considered as environmental contaminants [19,20].

With our method which did not take into consideration the breath flow because of ambulatory easy-to-use equipment-the measurement of ethanol in breath was not considered to be reliable [21]. Acetone is reported to be a potential marker in clinical practice [22]. 2-methylbutane (isopentane) may be found in human breath [23]. 1,3 pentadiene can be produced by fungus belonging to human gut microbiota [24]. Dimethylcyclopropane (DMCP) is a well-known by-product of gut microbiota [25]. 1-propanol is relevant to measure the impact of fasting [26] or in lung cancer [27]. Toluene is a well-known interesting gas for detection of severe human diseases [28]. High yield of various phenols are produced by gut bacteria [29]. These gases are therefore selected for statistical analysis.

Statistics

The first group includes patients with SIBO, PO and a medical history of cancer. The second group includes patients with SIBO+PO without a medical history of cancer. In order to avoid large inter-individual fluctuations, gases with limited changes between T_0 and T_2h were identified and ratios were calculated using VOCs with broad magnitude (broad VOC) as numerator and VOCs with mild magnitude (low VOC) as denominator. The following gazes were detected by the SPME-GC-SM analysis: ethanol, acetonitrile, dichloromethane, ethylacetate, phenylethanol, M-xylene, 2-propanol, P-cymene, acetone, 2-methylbutane (isopentane), 1,3 pentadiene, dimethylcyclopropane, 1-propanol, toluene and phenol. Only acetone, 2-methylbutane (isopentane), 1,3 pentadiene, dimethylcyclopropane, 1-propanol, toluene and phenol were further analysed.

Gases were split into two groups. The first group includes gazes with broad (broad VOC) inter-individual fluctuation at T_0 or at T_2 hours (standard deviation>2 means): 2-methylbutane (157,907 ± 415,878), dimethylcyclopropane (85,839 ± 307,163) and acetone (569,139 ± 1,673,014). The second group of gazes includes gazes with low (low VOC) inter-individual fluctuations at T_0 or T_2 hours: 1,3 pentadiene

(60,356 ± 75,821), 1-propanol (10,147 ± 17,364), toluene (55,297 ± 65,925) and phenol (58,617 ± 98,145).

Ratios of broad VOC/low VOC were compared between group 1 and group 2. (Comparison of means) Calculations were performed for T_0, for T_2 and for differences between T_0 and T_2. Comparisons of means were performed using independent samples T tests. Since the number of patients in group1 is below 30, a Student-Fisher T-test was chosen. Specificity, false positive ratio, negative predictive value and positive predictive value and ROC curve were calculated for relevant parameters (D/TPPP).

Results

65 patients were included: 12 in group 1 (Table 1) and 53 in group 2 (Table 2). Mean of broad VOCs/low VOCs ratios were compared between group1 and group 2 (Table 3).

The most reliable ratios to differentiate the 12 groups were dimethylcyclopentane/(toluene+phenol+1propanolol+pentadiene) (D/TPPP) either for T0 (0.50 ± 0.26 *versus* 0.28 ± 0.17; p<0.01) or for the difference between T_0 and T_2 (0.15 ± 0.21 *versus* -0.07 ± 0.20; p<0.001).

All 65 patients were classified according to the ratio D/TPPP. The sensitivity and the false positive rate were calculated. The figure 1 shows the ROC curve for the ratio D/TPPP. The threshold is close to 0. The sensitivity is equal to 75% and the false positive rate is equal to 31.25%. The negative predictive value is equal to 91.7% and the positive predictive value is equal to 96.4%. Patients in group1 had a higher plasmatic concentration of HA (78.3 ± 40.5 microg/l *versus* 37.7 ± 19.6; p<0.001). Patients in groups 1or 2 have high and similar percentage of infection with *Helicobacter pylori* (HP) (respectively 41.7% and 49.1%; p<0.05) or of clinical herpes simplex (58.8% *versus* 48%, p<0.05).

Table 1: Patients with SIBO+PO and cancer (group 1; 12 patients).

Patients	Clinical Herpes simplex	Plasmatic Hyaluronic acid (µg/l)	*Helicobacter pylori*	Diseases
1	Yes	105	Yes	Thyroid cancer
2	Yes	75	No	Colonic cancer
3	Yes	32	Yes	Colonic cancer
4	Yes	58	Yes	Prostatic cancer
5	Yes	109	Yes	Breast cancer
6	Yes	78	No	Carcinoma of the uterine cervix
7	Yes	68	No	Thyroid cancer, carcinoma of the uterine cervix
8	No	35	No	Thyroid carcinoma
9	Yes	171	No	Prostatic cancer
10	Yes	89	Yes	Colonic cancer
11	No	25	No	Giant cell tumour of the knee
12	No	95	No	Thyroid cancer
Mean or number	9	78.3	5	
SD or %	75%	40.5	41.7%	

Patients with SIBO (Small Intestinal Bowel Overgrowth) + PO (Periodontitis) + medical history of cancer (mainly adenocarcinoma). Hyaluronic acid levels are high; almost twice the normal range (40 µg/l).

Discussion and Conclusion

Concerning VOC detection

PO has been attributed to specific types of bacteria [30,31] and is associated with an increased risk of cancers [2,3].

Bacterial signature may be identified by breath tests focused on VOC [32-35]. Early detection of some cancers may also be detected by exhaled VOC [7-12].

In this epidemiological retrospective analysis, the ratio of DMCP/TPPP was higher in patients with a medical history of cancer (p<0.001). The sensitivity (75%), the false positive rate (31.25%), the negative predictive value (91.7%) and the positive predictive value (96.4%) of the ratio D/TPPP are satisfactory, as far as simple screening is concerned. This is the first time that a link between DMCP and a medical history of cancer is reported.

DMCP is derived from cyclopropane ring which occurs only in organisms that synthesize specific unsaturated fatty acids (UFA). Cyclopropane Fatty Acids (CFA) are typically produced at the onset of the stationary phase in bacterial cultures [36]. The timing and extent of the UFA-to-CFA conversion and the widespread distribution of CFA synthesis among bacteria suggest an important physiological role for this phenomenon [25,36].

The following bacteria may produce CFA: i.e. *Arthrobacter, Alcaligenes, Azotobacter, Bifidobacterium, Bordetella, Campylobacter, Caulobacter, Clostridium, Chlorobium, Citrobacter, Enterobacter, Helicobacter, Klebsiella, Lactobacillus, Nitrobacter, Pediococcus, Proteus, Pseudomonas, Rhizobium, Salmonella, Serratia, Streptococcus, Thiobacillus, Vibrio, Yersinia* [25].

Some bacteria can be excluded since there are mainly found in soil, used in food processing or are opportunistic bacteria which develop only in severely immunosuppressed patients: *Arthrobacter, Alcaligenes, Azotobacter, Bifidobacterium, Citrobacter, Lactobacillus, Nitrobacter, Pediococcus, Rhizobium, Serratia or Thiobacillus*. Other bacteria can also be excluded since they induce severe acute infections and since the included patients did not have any acute infection when enrolled: i.e. *Bordetella,Salmonella, Vibrio, and Yersinia*.

Some bacteria are either commensal or induce acute infections or intoxications. There implication in chronic infections has never been documented: i.e. *Clostridium, Enterobacter, Klebsiella, Proteus, Pseudomonas or Streptococcus* [37].

Campylobacter or Helicobacter are the only remaining possible candidates.

Numerous publications have causally implicated HP or *Campylobacters* [38,39], in the occurrence of PO. HP synthetizes 19:0 cyclopropane [40].

97% of *Campylobacter jejuni* strains and 83% of *Campylobacter coli* strains are characterized by the presence of a 19-carbon cyclopropane fatty acid. Others *Campylobacters* (including *Campylobacter rectus*) lack 19-carbon cyclopropane [41,42].

Because the percentage of HP is similar between the two groups of patients, we hypothesize that *Campylobacter jejuni* or *Campylobacter coli* could explain the higher rate of dimethylcyclopropane in patients with a medical history of cancer.

Concerning hyaluronic acid levels

Patients in group1 have a higher plasmatic concentration of HA (78.3 ± 40.5 microg/l *versus* 37.7 ± 19.6; p<0.001). We reported in

Table 2: Patients with SIBO+PO, without cancer (group 2; 53 patients).

Patients	Clinical herpes simplex	Plasmatic Hyaluronic acid (µg/l)	*Helicobacter pylori*	Diseases
1	No	58	Yes	Severe metabolic syndrome (myocardial infarctions, NASH)
2	No	95	No	Severe metabolic syndrome (diabetes, NASH)
3	No	12	Yes	Parkinson's disease, psoriasis, thyroiditis
4	No	50	No	Severe metabolic syndrome (diabetes, NASH)
5	Yes	26	No	NASH
6	Yes	34	Yes	Helicobacter pylori
7	Yes	12	No	Esophagitis
8	No	65	Yes	Thyroiditis
9	Yes	16	No	Urticaria, eczema, herpes, alcohol
10	No	18	Yes	Untreated dental cavities, oral aphtous lesions
11	Yes	35	No	Mild COPD, eczema
12	No	37	Yes	Thyroiditis, eczema
13	No	50	No	Colonic diverticulosis
14	No	71	Yes	Toxic extrapyramidal disorder
15	Yes	30	Yes	Overweight
16	Yes	48	Yes	Osteoporosis, gastro duodenal ulcer
17	Yes	65	Yes	Mild liver steatosis, severe acne
18	No	25	Yes	Vitiligo, allergy
19	No	22	No	Zona, alcohol
20	No	42	Yes	Severeacne (isotretinoin), psoriasis
21	Yes	19	No	Thyroiditis
22	No	35	Yes	Fibromyalgia, psoriasis
23	No	12	No	Diverticulosis, thyroiditis
24	Yes	28	Yes	Psoriasis, furonculosis
25	Yes	50	No	Controlled HIV, urticaria
26	Yes	19	No	Severe herpes, migraine
27	Yes	45	Yes	Overweight, psoriasis,acne, oral aphtous lesions
28	No	12	Yes	Vitiligo
29	No	56	Yes	Overweight, endometriosis, chronic rhinosinusitis.
30	No	26	No	Gougerot-Sjögren, atrophicthyroiditis, osteoporosis
31	No	12	Yes	Severe acne (isotretinoin), chronic rhinosinusitis
32	No	33	No	Controlled metabolic syndrome, no NASH
33	No	17	No	Psoriasis
34	Yes	36	No	Overweight, liver steatosis, no NASH
35	No	74	Yes	Thyroiditis
36	Yes	46	Yes	Liver steatosis, no NASH, mild psoriasis
37	Yes	39	No	Atrophic thyroiditis, pollen allergy
38	Yes	65	No	Eczema, osteopenia
39	Yes	14	Yes	Acne, nasal polyps
40	No	45	Yes	Asthma, steatorrhea
41	Yes	51	No	Diarrhea
42	No	12	No	Pollen allergy, overweight, liver steatosis
43	No	48	No	Asthenia, acne
44	No	33	No	Obesity, cardiac arrhythmia, glucose intolerance
45	No	48	Yes	Dysbiosis, abdominal pain
46	Yes	49	Yes	Mild psoriasis
47	No	38	No	Osteopenia, controlled Hashimoto's thyroiditis
48	No	9	Yes	Depression, liver steatosis
49	No	24	No	Liver steatosis, pollen allergy

50	Yes	56	No	Asthenia, mild depression
51	Yes	30	Yes	Eczema, severe gastro-oesophageal reflux
52	Yes	34	Yes	Urticaria, chronic rhinosinusitis
53	Yes	72	No	Dysbiosis, bloating, abdominal pain
Mean or number	24	37.7	26	
SD or %	45.3	19.6	49.1	

Patients with SIBO (Small Intestinal Bowel Overgrowth)+PO (Periodontitis) and no medical history of cancer. Hyaluronic acid levels are less than 40 µg/l.

Table 3: Comparison of ratios M/TPPP, D/TPPP, A/TPPP, (M+D)/TPPP, (D+A)/TPPP and (M+D+A)/TPPP between group 1 and group 2.

	Group 1 (12 patients)	Group 2 (53 patients)	P values
T_0			
M	0.82 ± 0.64	0.60 ± 0.57	> 0.05
D	**0.50 ± 0.26**	**0.28 ± 0.17**	**<0.01**
A	3.48 ± 3.46	2.26 ± 2.20	>0.05
M+D	1.24 ± 0.85	0.87 ± 0.69	> 0.05
D+A	3.91 ± 3.58	2.53 ± 2.25	>0.05
M+A	4.30 ± 3.95	2.86 ± 2.52	>0.05
M+D+A	4.73 ± 4.07	3.13 ± 2.59	>0.05
T_2 hours			
M	0.89 ± 0.87	0.73 ± 0.71	>0.05
D	0.34 ± 0.20	0.38 ± 0.24	>0.05
A	2.82 ± 2.61	1.9 ± 1.29	>0.05
M+D	1.22 ± 1.05	1.06 ± 0.90	>0.05
D+A	3.15 ± 2.73	2.23 ± 1.47	>0.05
M+A	3.71 ± 3.14	2.62 ± 1.75	>0.05
M+D+A	4.04 ± 3.28	2.95 ± 1.95	>0.05
T_0-T_2 hours			
M	-0.07 ± 0.23	-0.13 ± 0.14	>0.05
D	**0.15 ± 0.21**	**-0.07 ± 0.20**	**<0.001**
A	0.66 ± 0.85	0.37 ± 0.91	>0.05
M+D	0.02 ± 0.20	-0.19 ± 0.22	<0.01
D+A	0.76 ± 0.84	0.30 ± 0.78	>0.05
M+A	0.59 ± 0.81	0.24 ± 0.77	>0.05
M+D+A	0.69 ± 0.79	0.17 ± 0.65	>0.05

a preliminary study that an increased level of plasmatic HA is associated with an increased risk of adenocarcinoma in patients with severe PO [14].

Hyaluronidase activity has not been described either for *Campylobacter jejunior* for *Helicobacter pylori*. However, some strains of *Campylobacter jejuni* synthetize a hyaluronic acid-type capsular polysaccharide [43,44], which may modify the level of circulating HA.

Campylobacter jejuni is associated with SIBO and small gut motility decrease [45-46]. However, this bacterium has not yet been implicated in the occurrence of adenocarcinoma. [47,48]. To our knowledge *Campylobacter jejuni* has not been associated with PO.

Campylobacter rectus is associated with PO [30,31] and total cancer risk increase [48]. Since all *Campylobacters* may N-glycosylate their proteins [49], an involvement of *Campylobacter rectus* in the increase of plasmatic HA cannot be excluded. However, this latter bacterium does not produce dimethylcyclopropane.

To conclude, in patients with SIBO+PO and a medical history of cancer, plasmatic hyaluronic acid level is increased as well as exhaled dimethylcyclopropane concentration. The measure of VOC (especially DMCP) and of plasmatic hyaluronic acid level on a routine basis in patients with SIBO and PO could help to detect patients with a higher risk of cancer. The implication of *Campylobacter jejuni* or of *Campylobacter rectus* should be further investigated.

Acknowledgment(S) and Conflicts of Interest

No conflict of interest to disclose.

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