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Exhaled Volatile Organic Compounds in Patients with Colonic Polyps

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Abstract

Background: Exhaled Volatile Organic Compounds (E-VOCs) may help to early detection of colonic polyps.

Objective: Assess whether a new ambulatory device is able to detect specific E-VOCs in patients recently diagnosed with colonic polyps.

Material and Methods: All data were collected during routine consultations for Small Intestinal Bowel Overgrowth. A breath test was performed by X-PID 9500®.

Results: 203 patients older than 45 years of age were included. 31patients (15.3%) reported colonic polyps. 74 patients presented with gastroduodenal or jejunal (GDJ) liquid at ultrasound examination despite fasting.

96 patients (47.3%) exhaled numerous E-VOCs with a retention time between 12 to 45s (E-VOCs 12 to 45s). All patients of the polyp group exhaled E-VOCs 12 to 45s.

69 patients with GDJ liquid exhaled E-VOCS 12 to 45s. 11 patients out of these 69 cases (15.9%) present with polyps. 27 patients exhaled E-VOCs 12 to 45s and did not have GDJ, 20 of whom (74.1%) presented with polyps.

When GDJ liquid is not objectivised after fasting, the sensitivity of the E-VOCs 12 to 45s to identify patients with colonic polyps is equal to 100.0% and the specificity is 93.6%. The positive predictive value is 74.1% and the negative predictive value is 100%.

Conclusion: After fasting, X-PID 9500® is able to detect E-VOCs associated with colonic polyps, when GDJ liquid is excluded.

Keywords: Breath Test, Colonic Polyps, Chromatography

List of abbreviations:

Ac: acetate
BMI: Body Mass Index
E-VOCs: Exhaled Volatile Organic Compounds

GDJ: Gastro Duodena Jejunal
H_2: Hydrogen
H_2S: Hydrogen Sulphide
LMW-HA: Low Molecular Weight Hyaluronic Acid
NPV: Negative Predictive Value
OH-buty: Beta-hydroxyl-butyrate
PA: Propionibacterium Acnes
ppb: Parts Per Billion
PPV: Positive Predictive Value
RT: Retention Time
Se: Sensitivity
SIBO: Small Intestinal Bowel Overgrowth
Sp: Specificity
TUS: Transabdominal UltraSound examination
UC: Ulcerative Colitis.

Introduction

Imbalanced intestinal microbiota may favour chronic inflammation/destruction of mucosa vagal impairment as well as decreased immunity [1,2]. Intestinal microbiota can be studied by the analysis of exhaled gases [3]. Many authors reported links between specific exhaled volatile organic compounds (E-VOCs) and colorectal cancers [4,5]. Altered oral or gut microbiota may be responsible for chronic mucosal inflammation and destruction. For example *Fusobacterium nucleatum* proliferation may impair mucosal barrier or gut immunity and induce molecular alterations [6] or colonic adenocarcinoma [7].

We investigated whether a specific E-VOC or a range of E-VOCs detected with a new ambulatory device (X-PID 9500®) was associated with colonic polyps. A previous study [8] concluded that patients with vagal impairment (arrhythmia or gastroparesis) more frequently exhale specific E-VOCs and have a medical history of cancer/dysplasia. We took advantage of routine ultrasound examination to investigate gastro-duodeno-jejunal voiding.

Materials and Methods

This work is a descriptive retrospective epidemiological study. Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO) from 2022 March 1st to 2022 June 30th. 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 data collection. This retrospective analysis of Case Series cannot therefore be qualified 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). French legislation does not require the consent of an Institutional Review Board in such epidemiological studies.

Inclusion criteria: Patients consulting for SIBO and who underwent a breath test and a transabdominal ultrasound examination (TUS). Patients should have undergone a colonoscopy within the previous two years.

Patients signed a written consent for the possible retrospective use of the collected data. Patients should be older than 45 years of age.

Exclusion criteria: Ongoing tobacco abuse (which may interfere with E-VOCs) lack of TUS or colonoscopy lack of signed consent for possible retrospective epidemiological use of data recent intake of antibiotic therapy or of essential oils which may lead to mas-

sive destruction of the digestive flora and less than 1 ppm of total E-VOCs at the first measure after 10 hours of fasting uncontrolled endocrine disease (including thyroid insufficiency) incomplete information on drug or food complement intake.

Ultrasound examination: Gastroparesis was diagnosed when the stomach contained liquid or when its surface reached 10 cm^2 after 10 hours of fasting.

Lack of gastro-duodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic abdominal manoeuvres.

The duodenal should mainly contain bubbles after fasting. The mucosa is no visualized. The duodenal does not contain liquid. Jejunal hypotonia could also be implicated. In that case the jejunum contains liquid few bubbles and no peristalsis is visualized [9]. When liquid is detected in the stomach the duodenum or the jejunum the criterion "GDJ liquid" is fulfilled.

Propionibacterium Acnes (PA) on the Tongue: PA produces porphyrins which are fluorescent with ultraviolet light. This characteristic is used to follow acne and to quantify its severity [10]. We used a Wood lamp to assess the presence of PA of the tongue.

Gas Measurement: The patient comes after at least 10 hours of fasting. He /she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air of the lungs in a first neutral plastic bag (1.3 litre) and afterwards he/she exhales at least 100 ml (expected to belong to the expiratory reserve volume) in a small neutral plastic bag (Contralco® Gignac France www.contralco.com).

E-VOCs from the second bag are then immediately measured by the X-PID 9500® an ambulatory gas chromatograph associated with photoionization detection technology [Dräger Lubeck Germany www.draeger.com › Products › Multi-Gas-Detectors]. X-PID 9500® detects Volatile Organic Compounds (VOCs) concentrations as low as 15 ppb. Acetic propionic beta-hydroxybutyric (OH-buty) and butyric are detected within the first 7.9s pentane and hexane between 12.6 and 14.7s and toluene between 38.6 and 44.8 seconds.

X-PID 9500® does not detect hydrogen and is therefore not suitable for the detection of SIBO related to sugar-malabsorption. X-PID 9500® was used after breath holding and only after fasting not after sugar intake.

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am 8000® [Dräger Lubeck Germany www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen and hydrogen sulphide.

Both devices are easily portable and equipped with powerful pumps. Patients could be placed in separate rooms when necessary. The setup is basic and similar for both devices. It requires only a short neutral tube to connect the bag and the device. The results are quantified and directly exported in Excel tables.

Statistics: Comparisons of percentages or means used two-sample t-tests. Yates correction was used for small samples. Chi2 analyses were also performed when appropriate. The polyps group and control group were compared for E-VOCs TUS results and PA on the tongue. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p<0.001$.

Sensitivity false positive ratio negative predictive value and positive predictive value were calculated for the most relevant parameter.

Control Group: All eligible consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria was identified. As a consequence no recruitment or selection bias is expected. The control group is equal to the total number of included patients minus the polyps group. Classical demographic data will be compared. The control group appears appropriate.

Results

This descriptive epidemiological study includes 203 patients. 67.0% were female. All patients were Caucasian.

The median age of patients is 56 years of age. The minimal age is 45 (inclusion criteria) and the maximal age is 81. The first quartile is 45 years of age the third quartile is 65. This population sample appears appropriate for detection of colonic cancer. See (Table 1) for details.

Gender	Age (years of age)	Weight	Height	Body Mass Index	Patients previously treated with isotretinoin
67.0% female 33.0% male	Mean = 54.5 +/- 13.9 Median = 56 First quartile = 45 Third quartile = 65 Min = 45 Max = 82	65.3 +/- 16.3 kg	167.8 +/- 13.6 cm	22.6 +/- 4.2 kg/m²	15 7.4%

Table 1: Demographic data (203 patients all Caucasian). Percentage or mean+/-standard deviation

31 patients (15.3%) had a recent medical history of colonic polyps sometimes with dysplasia never with cancer. 21 patients presented with Crohn disease or UC. See (Table 2).

Crohn or UC	Colonic polyps	GDJ liquid	H_2	H_2S	Ac	Propio	OH-buty	Buty	Pics 12 to 45s	PA on tongue
21 10.3%	31 15.3%	74 36.5%	13.0 +/- 10.3	0.13 +/- 0.05	0.05 +/- 0.02 111 values Median = 0.05	always<0.02 50 values	1.56 +/- 4.5 Median = 0.9	0.70 +/- 0.60 44 values Median = 0.48	always<0.02 96 values	70 34.5%

Table 2: Digestive findings Number and percentage or mean+/-standard deviation. Gases concentrations are in ppm. Acetate propionate and butyrate were not detected in all patients (number of values are provided)

TUS detected liquid in the stomach the duodenum or the jejunum in 74 patients. This feature implies poor gastric emptying or duodeno-jejunal peristalsis. OH-buty and hydrogen (H_2) or hydrogen sulphide (H_2S) were always detected. Acetate (Ac) was detected in 111 instances propionate in 50 patients and butyrate in 44 patients respectively. E-VOCs 12 to 45s were detected in 96 patients (47.3%). The pics were always numerous and between 10 to 20 ppb.

OH-buty or butyrate strongly fluctuate between patients and does not follow a Gaussian distribution. The median value of OH-buty (0.9 ppm) was therefore chosen for further analysis. The median value of butyrate (0.48 ppm) was chosen for further analysis. PA on the tongue was visualized by a reddish fluorescence in 34.5% of patients. See Table2 for details. Patients with recent detection of colonic polyps always exhaled E-VOCs 12 to 45s (100% versus 37.8% $p<0.001$). They also exhaled more frequently low levels of OH-buty levels (19.4% versus 51.7% $p<0.001$). Eventually they present more frequently with PA on their tongue (54.8% versus 30.9% $p<0.001$). See (Table 3).

	≥50 years of age	<50 years of age	GDJ liquid	H_2	H_2S	Ac	Propio (%)	OH-buty> median	Buty> median	E-VOCs 12 to 45s	PA on tongue
Colonic polyps 31 cases	23 16.9%	8 11.9%	11 35.5%	13.1 + / - 11.6	0.12 + / - 0.04	0.04 + / - 0.02	7 22.6%	**6 19.4%**	3 33.3% 9 values	**31 100%**	**17 54.8%**
No colonic polyp 172 cases	103 83.1%	59 88.1%	52 38.2%	12.3 + / - 8.2	0.13 + / - 0.05	0.05 + / - 0.02	43 25.0%	**89 51.7%**	18 51.4% 35 values	**65 37.8%**	**54 30.9%**
P values	NA	NA	NS	NS	NS	NS	NS	**<0.001**	<0.01	**<0.001**	**<0.001**

Table 3: Polyps according to age GDJ liquid breath-test results or PA on tongue

NA: Not applicable. Please note firstly that 74.2% (23/31) of polyps are detected in patients older than 50 years of age and secondly that the percentage of detection of polyps is slightly superior in patients older than 50 years of age (16.9% versus 11.9% p<0.03 (trend)).

74.2% of polyps are detected in patients older than 50 years of age. However the percentage of detection of polyps is not statistically superior in patients older than 50 of age (16.9% versus 11.9%) although a trend is objectivised (p<0.03). No difference was found regarding H_2, H_2S acetate propionate butyrate or GDJ liquid. See Table3 for details. Age has no influence on H_2 H_2S Ac butyrate E-VOCs 12 to 45s levels or PA detection on the tongue. However GDJ liquid is associated with E-VOCs 12 to 45s PA detection on the tongue or low OH-buty levels. See (Table 4).

	H_2	H_2S	Ac	Propio 50 cases	OH-buty	OH-Buty >median 95 cases	Buty	E-VOCs 12 to 45s 96 cases	PA on tongue 70 cases
≥50 years of age 136 cases	12.3+/-8.2	0.13+/-0.05	0.05+/-0.02	37 27.2%	1.13 +/-1.16	61 44.9%	0.71 +/-0.6	66 48.5%	46 33.8%
<50 years of age 67 cases	14.3+/-13.5	0.13+/-0.06	0.04+/-0.02	13 19.4%	2.46 +/-7.8	34 50.7%	0.66 + / - 0.61	30 44.8%	24 35.8%
P values	NS	NS	NS	<0.001	<0.001	NS	NS	NS	NS
GJD liquid 74 cases	14.5+/-13.5	0.12+/-0.04	0.04+/-0.02	16 21.6%	1.62 +/-7.3	19 25.7%	0.59 + / - 0.43	69 93.2%	52 70.3%
No GJD liquid 129 cases	12.1+/-7.8	0.14+/-0.05	0.05+/-0.02	34 26.4%	1.52 +/-1.57	76 58.9%	0.83 +/-0.75	27 20.9%	18 14.0%
P values	NS	NS	NS	NS	NS	<0.001	NS	<0.001	<0.001

Table 4: Influence of age or of GDJ liquid on breath-test results or PA detection on the tongue

GDJ liquid should therefore be taken into consideration for further analysis although it is not *per se* associated with colonic polyps. Interestingly age and BMI have no influence on GDJ liquid. See (Table 5).

	Age	BMI	Colonic polyps 31 cases		No colonic polyps 172 cases	
			E-VOCs 12 to 45s	No E-VOCs 12 to 45s	E-VOCs 12 to 45s	No E-VOCs 12 to 45s
GDJ liquid 74 cases	55.2 +/- 14.0	23.3 +/- 4.9	11 14.9%	0 0%	**58 78.4%**	**5 6.8%**
No GDJ liquid 129 cases	54.1 +/- 19.8	22.2 +/- 3.75	20 15.5%	0 0%	**7 5.4%**	**102 79.1%**
P values	NS	NS	NS	NS	**<0.001**	**<0.001**

Table 5: DJ liquid according to age BMI colonic polyps pics 12 to 45s or PA on tongue

20 patients presented with colonic polyps and E-VOCs 12 to 45s without presenting with GDJ liquid. In contrast no patient presented with polyps when E-VOCs 12 to 45s is not detected. Only 7 patients presented with E-VOCs 12 to 45s without GDJ liquid and without polyps. See (Table 6).

		E-VOCs 12 to 45s	No E-VOCs 12 to 45s
Colonic polyps	GDJ liquid	11	0
	No GDJ liquid	20	0
No colonic polyps	GDJ liquid	58	5
	No GDJ liquid	7	102

Table 6: Detection of E-VOCs 12 to 45s according to colonic polyps and GDJ liquid Number of cases

Consequently E-VOCs 12 to 45s could be a good marker for the detection of colonic polyps in patients without GDJ liquid. The sensitivity of the E-VOCs 12 to 45s is then equal to 100.0%. The specificity is 93.6%. The positive predictive value is 74.1% and the negative predictive value is 100%. See (Table 7).

	Colonic polyps	No colonic polyps	Se§ Sp PPV NPV
E-VOCs 12 to 45s positive	20 (a)	7 (b)	**Se= 100%** **Sp= 93.6%** **PPV= 74.1%** **NPV= 100%**
E-VOCs 12 to 45s negative	0 (c)	102 (d)	

Table 7: Sensibility specificity PPV NPV of E-VOCs 12 to 45s to detect colonic polys in patients without GDJ fluid at TUS examination (129 patients).

§Se=a/(a+c)Sp=d/(b+d)PPV=(Se*prevalence)/(Se*prevalence+(1-prevalence)*(1-Sp))

NPV=Sp*(1-prevalence)/(Sp*(1-prevalence)+prevalence*(1-Se)) prevalence=(a+c)/(a+b+c+d)

GDJ liquid which is associated with E-VOCs 12 to 45s decreases the specificity of these E-VOCs for the detection of colonic polyps. E-VOCs 12 to 45s are more present when PA is detected on the tongue see (Table 8) and when OH-butyrate is low see (Table 9). PA on the tongue is however not correlated with OH-buty levels see (Table 8).

	OH-buty >median 95 cases	E-VOCs 12 to 45s 96 cases
PA of tongue 70 cases	27 38.5%	**41** **58.6%**
No PA of tongue 133 cases	68 51.3%	**29** **21.8%**
P values	NS	**<0.001**

Table 8: PA on tongue according to OH-buty levels or pics 12 to 45s

	E-VOCs 12 to 45s 96 cases	No E-VOCs 12 to 45s 107 cases
OH-buty >median 95 cases	24	71
OH-buty ≤median 108 cases	72	36

Table 9: Inverse association between OH-levels and Pics 12 to 45s

P value (Chi square)<0.001

	Medical history of severe acne		No or mild to moderate previous acne 163 cases
	Isotretinoin use 15 cases	No isotretinoin use 25 cases	
Colonic polyps 31 cases	0	6	25
No Colonic polyps 172 cases	15	19	138
P values (Chi square)	NS (p<0.05)		NS*
E-VOCs 12 to 45s 96 cases	1**	15	80
No E-VOCs 12 to 45s 107 cases	14	10	83
P values (Chi square)	P<0.001		NS*
GDJ liquid 74 cases	5	10	59
No GDJ liquid 129 cases	10	15	104
P values (Chi square)	NS		NS*
OH-buty>median 95 cases	7	12	76
OH-buty≤median 108 cases	8	13	87
P values (Chi square)	NS		NS*

Table 10: Colonic polyps pics 12 to 45s GDJ liquid and OH-buty levels according to previous severe acne (with or without a medical history of isotretinoin intake)

*When compared with severe acne not treated with isotretinoin **Patient with Crohn's disease

15 patients had a medical history of severe acne treated with isotretinoin. 25 patients experienced severe acne and did not receive isotretinoin. Others did not complain of severe acne (163 patients). Except for E-VOCs 12 to 45s and only between the patients with a medical history of severe acne previously treated with isotretinoin or not treated with isotretinoin ($p<0.001$) no difference was detected between the groups with or without colonic polyps (trend with $p<0.05$) GDJ liquid or high OH-buty levels. See (Table 10).

We concluded that isotretinoin may decrease one or several conditions which favour the occurrence of E-VOCs 12 to 45s and perhaps the development of polyps.

Discussion

Early detection of colonic polyps is an undisputed international public health problem. The French Public Health Authority considers age as the major risk factor and recommends starting screening for colorectal carcinoma in patients above 50 years of age [11].

However, in this cohort age does not appear to be the most relevant physiological parameter influencing the occurrence of colonic cancer. In this cohort the most relevant parameters associated with colonic polyps are E-VOCS 12 to 45s low OH-buty or PA on the tongue.

Breathe Test: E-VOCs 12 to 45s and OH-butyrate. A significant association has been found between E-VOCs 12 to 45s and colonic polyps.

This association increases when GDJ dysfunction is excluded by TUS. In that case the sensitivity of the E-VOCs 12 to 45s to identify patients with colonic polyps is 100%. The specificity is 93.6%. The positive predictive value is 74.16% and the negative predictive value is 100%. It can be therefore concluded that patients presenting with E-VOCS 12 to 45s and without GDJ liquid should be classified as "highly at risk patients" and should undergo colonoscopy regularly.

E-VOCs 12 to 45s are not associated with age and are inversely associated with GDJ liquid which is itself not related to age or BMI. OH-butyrate levels - a marker of ketogenesis and fasting [12] - are logically inversely correlated with GDJ liquid. As expected OH-butyrate levels are inversely associated with E-VOCs 12 to 45s.

GDJ liquid could be a clinical sign of failure of fasting despite no food intake for 10 hours. OH-buty appears to be a marker of adequate GDJ emptying during fasting. Since the foregut does not contain sugars anymore the ketogenic cycle starts and hydroxybutyrate is produced. E-VOCs 12 to 45s may be produced by bacteria proliferating in the foregut and therefore in patients with detecTableGDJ liquid. Pentane detection has been associated with UC [13]. Pentane belongs to E-VOCs 12 to 45s. UC is a well-recognized risk factor of digestive cancer/dysplasia [14].

Autophagy through the cleaning of inflammatory bacteria or fungi controls the quality of the digestive microbiota [15]. A positive feedback by small chain fatty acids produced by bacteria stimulates autophagy [16]. E-VOCs 12 to 45s may be a marker of altered autophagy or altered apoptosis. However we found no published data on specific E-VOCs 12 to 45s associated with altered autophagy. In our cohort exhaled acetate propionate and butyrate were very low and mainly replaced by OH-butyrate. Dysbiosis associated with small-chain-fatty-acids-producing bacteria is therefore excluded. Since PA is expected to produce propionic acid – which was rarely detected and only at low levels - a key role of PA in the microbiota responsible of inflammation is excluded.

TUS: TUS enables to diagnose GDJ emptying impairment and dramatically enhances the liability of E-VOCs 12 to 45s to predict the detection of colonic polyps. GDJ liquid is a better marker than OH-buty levels although GDJ liquid in inversely correlated with low OH-buty levels. This finding suggests that ketogenosis is less informative than disturbance of the foregut voiding. We hypothesize that mucosal or vagal disturbances – perhaps associated with noxious deposits and chronic inflammation - are more important than deficiencies due to small gut malabsorption of nutriments with regard to the occurrence of colonic polyps.

Vagal impairement: We previously reported that gastroparesis is associated with specific E-VOCs [17]. In animal experiments vagal impairment may induce altered-T-regulation leading to colitis [18]. We hypothesized that E-VOCs 12 to 45s could either be a marker of vagal impairment or of inflammation of gastroduodenal mucosa either primary or secondary to food/liquid stagnation.

In this cohort GDJ liquid is not associated with an increased risk of polyps when E-VOCs is not present. Patients with selective vagotomy are at high risk to develop colonic polyps [19]. However we did not find any reference or published hypothesis directly implicating vagal impairment in the occurrence of colonic polyps. Dysbiosis in the liquid of the foregut or altered GDJ mucosa harbouring specific microbiota leading to leaky gut chronic inflammation –and afterwards vagal impairment - may explained E-VOCs 12 to 45s and may lately increase the risk of gastric and or colonic mucosal alteration. Overweight is associated with an increased risk of gastrointestinal cancers [20] and increased levels of E-VOCs [17]. It is noteworthy that acetate is decreased in patients with dysplastic polyps or colorectal cancers [21]. In such patients E-VOCs are expected to be elevated [8].

Propionibacterium acnes (PA): PA is frequently involved in acne [22]. Acne has been called "The metabolic syndrome of the pilosebaceous follicle" [23] and implicates the PI3/AKT/mTORC1 pathway in Paneth cell and skin or gut stem-cells in order to intake calories and therefore accumulate fatty acids [24]. PA which requires lipid and acidic conditions could take advantage of this local accumulation of lipids especially in Western countries with unhealthy diets [24]. Detection of PA on the tongue may therefore be a marker of overproduction of small chain fatty acids with accumulation in the mucosa or the in the submucosa of the foregut including the tongue. GDJ liquid despite fasting is associated with RGO and acidic condition in the mouth enhancing the ability of PA to eliminate concurrent biofilms less acidic-resistant. Human enterotypes have been classified into three groups. PA belongs to the Prevotella-enterotype - especially in case of severe periodontitis. This enterotype includes Helicobacter pylori and Desulfovibrio species [25].

PA alone may perhaps not *per se* favour gut inflammation. However other associated bacteria belonging to the Prevotella-enterotype may induce mucosal inflammation. There is no argument for any jejunal adverse effect induced by PA or by bacteria from the Prevotella-enterotype. PA does not appear to favour colonic polyps. However since PA may be a causal agent of UC and since UC is a well-documented condition increasing the risk of colonic polyps PA may be an indirect causative agent.

PA could only be a marker of a mucosal modification or of inappropriate GDJ emptying or both. It is probably not the triggering agent for fatty acids deposit in the mucosa. PA may only be opportunistic and afterwards may participate to mucosal damage and chronic inflammation. GDJ emptying disturbance or OH-buty decrease may be accelerating factors. Ketogenosis (OH-buty synthesis) contributes to intestinal cell differentiation and therefore appropriate absorption [26]. We hypothesised that malabsorption (due to excessive sugar intake or to mucosal injury) favours GDJ emptying dysfunction and E-VOCs synthesis leading to fatty acid accumulation in mucosa enabling PA invasion.

Isotretinoin in this cohort E-VOCs 12 to 45s is decreased in patients with a medical history of isotretinoin intake. Isotretinoin is known to modify duodenal and ileal mucosa [27] and has been implicated with severe malabsorption [28]. According to Melnik BC [29] the unifying mechanism of all isotretinoin-induced adverse effects is the apoptosis of stems cells which involves neural crest cells (explaining teratogenicity) hippocampal neurones (depression) epidermal keratinocytes and mucosa cells (muco-cutaneous side-effects) hair follicle cells (telegenic effluvium) intestinal epithelial cells (inflammatory bowel disease) skeletal muscle cells (myalgia and release of creatine kinase) or hepatocytes (release of transaminases and very low-density lipoproteins).

In animals' isotretinoin may decrease the risk of colonic polyps or experimental colonic cancers [30]. This preventive effect has not been confirmed in this epidemiological study possibly perhaps because of the lack of power. However, a trend has been found and the data are not in contradiction with the animal experimental results. Isotretinoin is not expected to improve vagal function or GDJ voiding. We hypothesised that hyperactivation of the mTORC1 pathway is probably the cornerstone and the preliminary step of mucosal disturbance leading to E-VOCs synthesis and GDJ emptying abnormalities.

Limitations of the Study

This cohort is based on gas analysis 10 to 14 hours after a light dinner. Some patients have GDJ liquid which suggest that-according to their physiology- at least some are actually not fasting. In such instance innocuous substances known to favour GDJ voiding and with an immediate effect could have been used to wash-out the GDJ liquid-effect.

This small cohort lacks power to further explore the possible negative impact of previous episodes of severe acne on E-VOCs 12 and 45s and the possible positive effect of isotretinoin either on E-VOCS 12 to 45s or on colonic polyps. Improvements of the method have been implemented and further collection of data is ongoing.

Application of this New Knowledge for Routine Practice

In practice breath tests with X-PID 9500® and TUS to look for GLD liquid should be routinely performed. Transabdominal ultrasound examination is an innocuous inexpensive and quick method to check for gastroparesis jejuno-duodenal reflux vagal hypertonia (reduced jejunal diameter) vagal hypotonia (increased jejunal diameter) or ileal break [9] and should be more frequently used by gastroenterologists to control digestive motility. The liability of X-PID 9500® results coupled with ultrasound examination findings is high enough to plea for the use of these techniques on a routine basis.

Patients with E-VOCs 12 to 45s-especially those without GDJ liquid-should be considered at high risk of polyps and should undergo a colonic exploration. This test could also be implemented to measure the duration of fasting that is required to see the disappearance of E-VOCs 12 to 45s and of GDJ liquid. It could help to build standards regarding GDJ emptying and quality of vagal activity.

Eventually it can help define customized regimens that can prevent the occurrence of E-VOCs 12 to 45 s and therefore ultimately prevent the occurrence of colonic polyps - in case of a causal relationship between E-VOCs 12 to 45s and polyps is confirmed.

Conclusion

All patients with colonic polyps exhale E-VOCs 12 to 45s.The detection of these gases can be performed in ambulatory practice within few minutes. The sensitivity of the test is very high (100%). The specificity can be improved when a TUS is concomitantly performed (93.6%).Both procedures are innocuous and inexpensive and may provide additional relevant medical pieces of information.

Patients with E-VOCs 12 to 45s-especially those without GDJ liquid- should be considered at high risk of polyps and should undergo a colonic exploration.

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