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Exhaled Volatile Organic Compounds and Vagal Tone are Different in Patients with Overweight or with Obesity: Practical Consequencies

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Abstract

Background: Urinary Volatile Organic Compounds have been associated with *type 2 diabetes mellitus* and overweight and may correlate with Exhaled Volatile Organic Compounds (E-VOCs).

Objective: We investigated whether a new ambulatory device is able to detect specific E-VOCs in patients with overweight (25≤Body Mass Index (BMI)≤30) or obesity (BMI>30). We further analysed to which physiological conditions these specific E-VOCs are associated.

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

Results: 685 patients were included. 150 patients belong to the overweight (OW) group and 44 belong to the obesity (OB) group. 491 patients have a BMI<25 and form the lean group.
Patients of the OW group present with jejunal decreased motility plus decreased mucosal thickness at ultrasound examination. An increased level of serum low-molecular-hyaluronic acid was also evidenced.
Patients of the OB group exhale more frequently low molecular weight E-VOCs (especially cluster 4 to 5.9s including acetate) and present with decreased jejunal diameter (vagal hypertonia) with preserved mucosa. Crohn's disease or ulcerative colitis (UC) was never associated with obesity.

We hypothesize that overweight and obesity are different diseases. There is no continuum.

Conclusion: Overweight and obesity may be different diseases. Combined breath analysis by X-PID 9500® and ultrasound examination are performant enough to distinguish them physiologically. They may help early diagnosis and treatment optimization.

Keywords: Breath test; Metabolic syndrome; Chromatography

List of abbreviations: BMI: Body Mass Index; Crohn: Crohn's disease; CMV: Cytomegalovirus; COVID-19: Coronavirus Disease; E-VOCs: Exhaled Volatile Organic Compounds; GLP-1: Glucagon like peptide 1; HPV: Human papillomavirus; HRV: Heart rate variability; LMW-HA: Low molecular weight hyaluronic acid; NASH: Non-alcoholic steatohepatitis; NLR: neutrophil-lymphocyte ratio; NPV: Negative predictive value; OB: obesity; OW: Overweight; PPV: Positive predictive value; RT: Retention time; SCFA: Small chain fatty acids; Se: sensitivity; SIBO: Small Intestinal Bowel Overgrowth; Sp: Specificity; T2DM: type 2 *diabetes mellitus*; UC: Ulcerative Colitis

Introduction

Imbalanced intestinal microbiota may favour overweight or obesity, type 2 *diabetes mellitus* (T2DM) [1,2], chronic inflammation/destruction of mucosa, vagal impairment, as well as decreased immunity [3,4].

Mild overweight and obesity could be either a continuum with a progressive increase in visceral fat and consequently with an increased risk of T2DM or visceral inflammation such as non-alcoholic steatohepatitis. They may also be different entities with different gut dysbiosis and different medical consequences. To our knowledge this latter hypothesis has never been addressed.

Intestinal microbiota can be studied by the analysis of exhaled gases such as hydrogen or methane [5-8] after the intake of sugars.

However, Volatile Organic Compounds (VOCs) appear to be more interesting markers and many authors reported links between specific faecal, urine or Exhaled-VOCs (E-VOCs) with diabetes [9-11]. Urinary or faecal specific VOCs have also been associated with overweight/obesity [12,13].

However, specific E-VOCs in overweight/obesity have not been documented in ambulatory practice.

In contrast, the link between specific E-VOCs and cancers [14-23] is extensively documented.

Similarly, specific E-VOCs are possibly related to gut-TH1-immunosuppression and consequently are associated with opportunistic infections such as mild COVID-19 [24].
COVID-19 infects more frequently patients with T2DM or overweight [25,26].

Overweight or obesity has been associated with an increased risk of cancer [27-32]. Specific E-VOCs could therefore be more frequently detected in patients presenting with high Body Mass Index (BMI).

T2DM has been associated with gastroduodenal voiding disturbances possibly due to alteration of vagal tone or of myenteric plexus activity [33,34].

Numerous gastrointestinal hormones, especially Glucagon like peptide 1 (GLP-1) produced by the ileum, regulate the voiding of the stomach and have been implicated in overweight/obesity [35].

However, dysbiosis may be the key factor for weight increase and E-VOCs could be a valuable test for screening or surveillance.

E-VOCs may also be a marker of inflammation, destruction of functional tissues and its consequences such as cancer or precancerous lesions.

E-VOCs may anyway help to detect early predisposing medical or physiological conditions as well as early complications.

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 overweight or obesity.

We also investigated whether signs in favour of immunosuppression, mucosal destruction or altered vagal tone were associated with overweight or obesity.

We collected data which may be related to: 1) TH1-immunosuppression (opportunistic infections such as herpetic flares, IgG against cytomegalovirus (CMV) or mild COVID-19, 2) mucosal destruction (serum LMW-HA levels, Crohn's disease, ulcerative colitis, or nickel allergy), 3) vagal impairment (gastroparesis, arrhythmia, osteopenia, and depression).

Heart rate variability (HRV) is a recognized marker of vagal tone [36,37]. Gastric emptying correlates with HRV [38]. Abdominal ultrasound is routinely performed in all patients coming for Small Intestinal Bowel Overgrowth (SIBO). We took advantage of the ultrasound examination to investigate gastric, jejunal and ileal movements, as well as jejunal mucosa [39,40].

Materials and Methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations for SIBO, from 2020 March 1st to 2020 October 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 the work has already been done. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not require approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria

Patients consulting for SIBO and who underwent a breath test.
Patients should provide with a full medical history, especially regarding cancer and precancerous lesions, herpes simplex, herpes zoster, nickel intolerance, ulcerative colitis, depression, thyroid pathologies, auto-immune diseases, allergic reactions, arrhythmia, depression, osteoporosis, body weight and height, as well as diabetes mellitus.

CMV serology, serum hyaluronic acid level and transabdominal plus thyroid ultrasound examinations are routinely performed in patients consulting for SIBO.

Patients signed a written consent for the possible retrospective use of the collected data.

Exclusion criteria

Ongoing tobacco abuse (which may interfere with E-VOCs); lack of CMV serology or of serum hyaluronic acid dosage; lack of transabdominal ultrasound; lack of signed consent for possible retrospective epidemiological use of data; uncontrolled diabetes mellitus; lack of breath test or recent intake of antibiotic therapy or of essential oils leading to massive destruction of the digestive flora or less than 2 ppm of E-VOCs at the first measure, after 10 hours of fasting; uncontrolled endocrine disease (including thyroid insufficiency); incomplete data on drug or food complement intake.

Medical history of cancer or precancerous lesions

All types of cancer or dysplasia were included. Lesions should have been histologically documented. As a consequence, non-dysplastic polyps were not included in the cancer group. Gallbladder polyps diagnosed by ultrasound examination were therefore not graded as dysplastic polyps.

Ultrasound examination

Gastroparesis was diagnosed when the surface of the stomach reached 10 cm2 after 10 hours of fasting. Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileocecal junction. 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 manoeuvers.

Jejunal hypotonia was diagnosed when jejunal diameter reaches 19.4 mm. In that case, the jejunum contains few bubbles, the mucosa is thin (≥1mm) and no peristalsis is visualized.

Decreased jejunal diameter (jejunal spasm attributed to vagal hypertonia) was considered when the measure drops under the threshold of 11.4mm [40,41].

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 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 50 ppb. Acetate, isobutylene and methylacetate are detected within 4 to 6.4 seconds; isobutyric, butyric, isovaleric and valeric acids between 7.0 and 7.9 seconds, toluene between 42 and 44 seconds, m-xylene or p-xylene between 90 and 97 seconds and o-xylene around 115 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 before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results will be published separately.

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. Chi-square calculation with Yates correction was used for small samples.

Lean group (25kg/m^2<BMI), overweight group (OW group; 25≤BMI≤30) and obesity group (OB group; BMI>30) were compared for clinical parameters and E-VOCs. Since peaks of E-VOCs may be numerous, we looked for clusters. A cluster contains several E-VOCs with close retention times and which are separated from other clusters by at least 1 second of retention time. A cluster is therefore a group of E-VOCs within a specific range of retention time, separated from other clusters and without overlapping.

Since E-VOCs and clinical diseases could be associated, additional comparisons of subgroups could be performed to identify dependent and independent variables. 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 E-VOCs cluster.

Control/lean group

All 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 OW and the OB group. The control group is named the lean group and appears appropriate to be the control group.

Classical demographic data will be compared.

Results

This descriptive epidemiological study includes 685 patients.

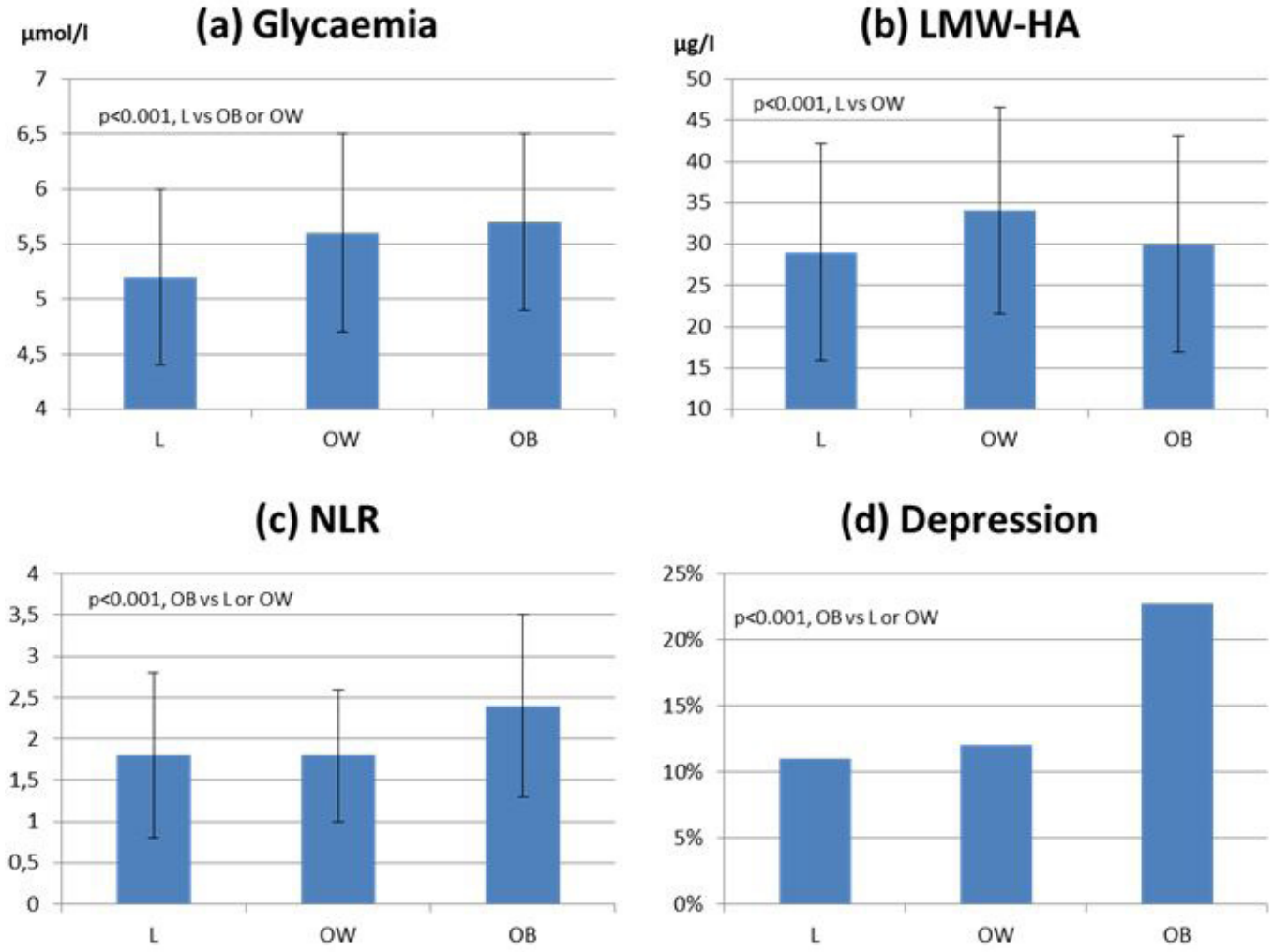
491 patients have a BMI lower than 25 kg/m² (lean group). 150 presented with overweight (25≤BMI≤30 kg/m²; OW group). 44 belong to the OB group (BMI>30 kg/m²).

Age and gender are similar in the three groups (Table 1).

	Lean group 491 patients	OW group 150 patients	OB group 44 patients	P value Lean versus OW	P value Lean versus OB	P value OW versus OB
Female patients	71.1%	56%	75%	<0.02	>0.05	>0.05
Age	53.5 +/- 12.0	53.0 +/- 12.5	51.3 +/- 4.2	>0.05	>0.05	>0.05

Table 1: Demographic data according to BMI

Glycaemia is lower in the lean group (5.2 +/- 0.8 µmol/l) and does not differ between OW group and OB group (5.6 +/-0.9 µmol/l versus 5.7 +/- 0.8 µmol/l) (Table 2 and Figure 1).
Therefore, obesity does not worsen glucose intolerance.



L= lean; OW= overweight; OB=obese

Figure 1: Key clinical or biological parameters which differ according to BMI **(a)** Glycaemia does not differ between OW group and OB group. Obesity does not worsen glucose intolerance. There is no continuum; **(b)** LMW-HA is increased in the OW group. Destruction of tissue is probable; **(c)** NLR is increased in the OB group which suggests chronic inflammation involving neutrophils; **(d)** Depression is more frequent in the OB group. Some types of depression have been attributed to chronic inflammation of the central nervous system

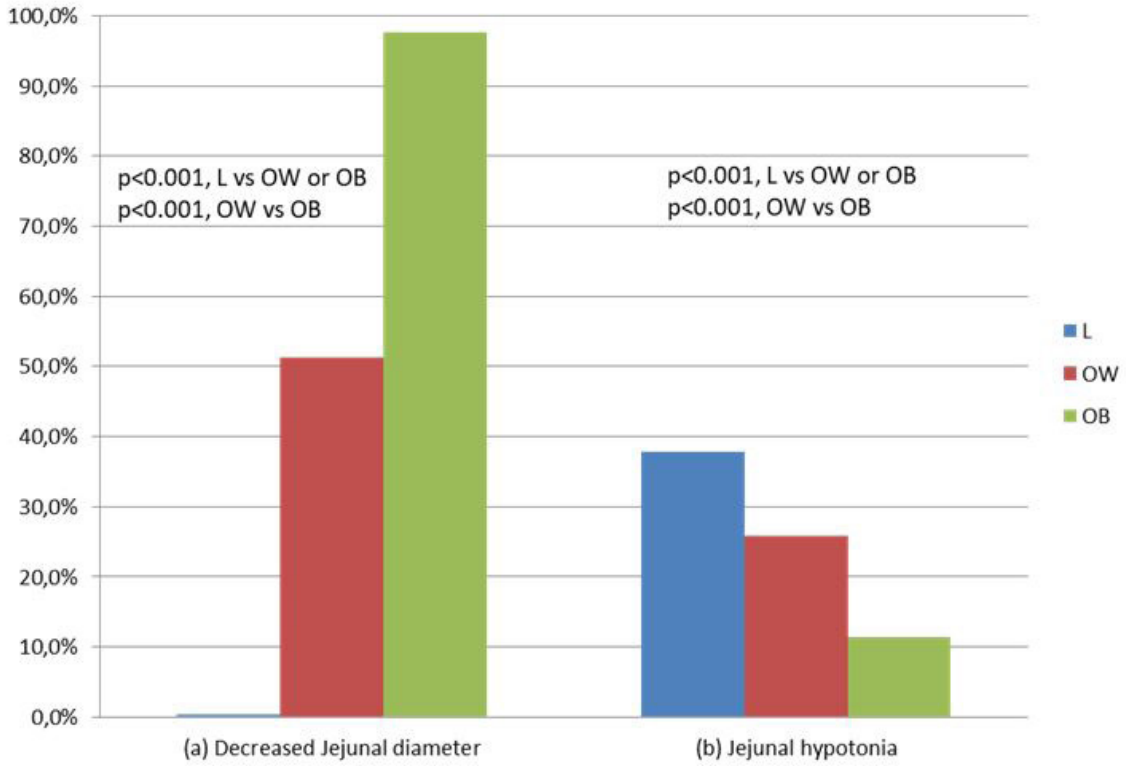
	Lean	OW	OB	P value Lean versus OW	P value Lean versus OB	P value OW versus OB
Glycaemia (µmol/l)	5.2 +/-0.8	5.6 +/-0.9	5.7 +/- 0.8	<0.001	<0.001	>0.05
NLR	1.8 +/-1.0	1.8 +/-0.8	2.4 +/-1.1	>0.05	<0.001	<0.001
Eosinophil count/mm³	183 +/-160	192 +/-148	122 +/-97	>0.05	<0.001	<0.001
Crohn/UC	6.9%	3.0%	0%	<0.001	<0.001	<0.001
Depression	11.0%	12.0%	22.7%	>0.05	<0.001	<0.001
LMW-HA (µg/l)	29.0 +/- 13.1	34.1 +/- 12.5	30.0 +/- 13.1	<0.001	>0.05	>0.05
Breast cancer	4.3%	2%	2.3%	<0.001	>0.05	>0.05
HPV-related dysplasia	4.1%	2.7%	2.3%	<0.001	>0.05	>0.05
Herpetic flare	42.8%	44.0%	20.4%	>0.05	<0.001	<0.001

Table 2: Relevant clinical and biological data which may be related to immunity, inflammation or destruction, according to BMI

The obese group is characterized by increased neutrophil-lymphocyte ratio (NLR), decreased eosinophil count, no Crohn's disease (Crohn) or ulcerative colitis (UC), high frequency of depression (table 2), decreased jejunal diameter (spasm) and rare jejunal hypotonia. Spasm (parasympathetic hypertonia) correlates with BMI and sky-rocketed up to 97.7% (Table 3 and Figure 2).

	Lean	OW	OB	P value Lean versus OW	P value Lean versus OB	P value OW versus OB
Decreased jejunal diameter	0.4%	51.3%	97.7%	<0.001	<0.001	<0.001
Jejunal hypotonia	37.9%	25.8%	11.4%	<0.001	<0.001	<0.001
Gastroparesis	15.3%	21.7%	13.6%	<0.001	>0.05	<0.02
Osteoporosis	8.1%	4.6%	4.5%	<0.001	<0.001	>0.05

Table 3: Relevant clinical data which may be related to vagal tone, according to BMI



L= lean; OW= overweight; OB=obese

Figure 2: Key ultrasound findings according to BMI **(a)** Decreased jejunal diameter can be attributed to parasympathetic hypertonia (spasm). It was almost always observed in obese patients and less frequently in overweight. There is a continuum between overweight and obesity; **(b)** Jejunal hypotonia (jejunal diameter ≥19.4 mm, no peristalsis, thin jejunal mucosa and few bubbles) can be attributed to myenteric plexus impairment. It is mainly observed in lean patients. There is a continuum between overweight and obesity

Overweight without obesity is characterized by a moderate increase of serum low-molecular weight hyaluronic acid (LMW-HA) and a slight increase of gastroparesis frequency. Serum LMW-HA was similar between the lean group and the OB group (Tables 2 and 3, and Figure 1).

A past medical history of breast cancer, HPV-related dysplasia and osteoporosis are associated with low body weight (Table 2).

There is no association between BMI and decreased anti-viral or anti-cancer immunity since increased incidences of CMV infection, COVID-19 infection or cancer are not observed in overweight or obese patients. Furthermore, herpetic flares are less frequently reported in the OB group (Tables 2 and 4).

Other parameters – nickel allergy, arrhythmia or autoimmunity – do not change according to BMI (Table 4).

	Lean	OW	OB	P value Lean versus OW	P value Lean versus OB	P value OW versus OB
Nickel allergy	5.7%	5.3%	6.8%	>0.05	>0.05	>0.05
COVID19 infection	4.1%	5.3%	2.3%	<0.01	<0.01	<0.01
CMV IgG	14.7%	11.3%	18.2%	<0.01	>0.05	<0.01
Digestive cancer or dysplasia	12.8%	11.3%	11.4%	>0.05	>0.05	>0.05
Arrhythmia	8.3%	8.3%	9.1%	>0.05	>0.05	>0.05
Auto-immunity **Thyroid** **Psoriasis**	 30.3% 17.3%	 26.8% 16.5%	 25.9% 13.2%	 >0.05 >0.05	 >0.05 >0.05	 >0.05 >0.05

Table 4: Non-relevant clinical data according to BMI

The following clusters of E-VOCs were identified: E-VOCs with retention time (RT) between 4 to 5.9s (includes acetate); E-VOCs with RT between 6 to 7.9s (includes propionate and butyrate); E-VOCs with RT between 8 to 9.9 s; E-VOCs with RT between 10 to 17.9s; E-VOCs with RT between 18 to 31.9s; E-VOCs with RT between 32 to 41.9s; E-VOCs with RT between 42 and 57.9s; E-VOCs with RT between 58 and 74.9s (cluster 58 to 74.9; including butyl acetate), E-VOCs with RT between 75 and 88.9s, E-VOCs with RT between 89 and 97s and E-VOCs with RT above 97s.

Cluster 89 to 97s is more frequently detected in the lean group.

Cluster 10 to 17.9s is more frequently detected in the OW group.

Cluster 4 to 5.9s is associated with the OB group (Table 5 and Figure 3). This cluster appears particularly interesting to distinguish between the microbiota of OB group and of OW group.

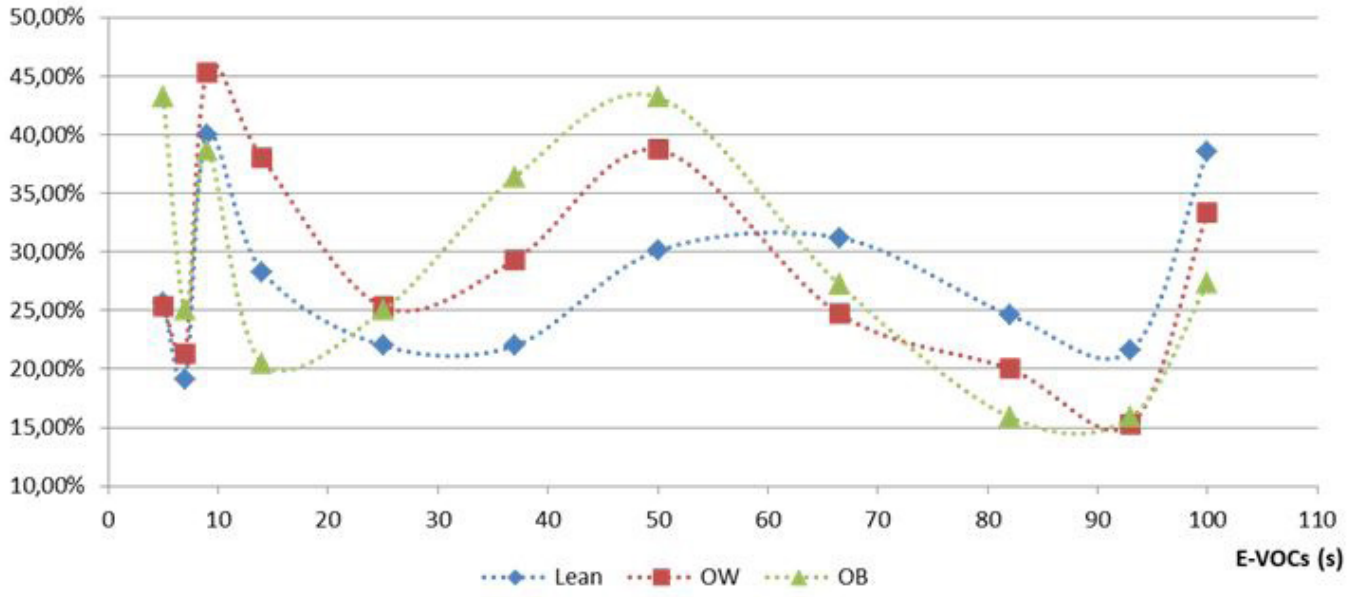


Figure 3: Frequencies of E-VOCs clusters according to BMI

Cluster 4 to 5.9s is associated with the OB group and enables to distinguish between the microbiota of OB group and of OW group.
Cluster 10 to 17.9s is more frequently detected in the OW group.
The OB and the OW curves cross the L curve in cluster 58 to 74.8s. E-VOCS could subsequently be split into two large sets: low molecular weight E-VOCs - rather associated with 4 to 5.9s and obesity – and high molecular weight E-VOCs – rather associated with tissue destruction, cancer, UC or vagal impairment.

Cluster 89 to 97s is more frequently detected in the lean group.

L= lean; OW= overweight; OB=obese

	Lean	OW	OB	P value Lean versus OW	P value Lean versus OB	P value OW versus OB
>97s	38.5%	33.3%	27.3%	>0.05	>0.05	>0.05
89 to 97s	21.6%	15.3%	15.9%	<**0.001**	>0.05	>0.05
75 to 88.9 s	24.6%	20%	15.9%	<0.05	<0.02	>0.05
58 to 74.9 s	31.2%	24.7%	27.2%	<0.02	>0.05	>0.05
42 to 57.9 s	30.1%	38.7%	43.2%	<0.02	<0.02	>0.05
32 to 41.9 s	22.0%	29.3%	36.4%	<**0.001**	<**0.001**	>0.05
18 to 31.9 s	22.0%	25.3%	25.0%	>0.05	>0.05	>0.05
10 to 17.9 s	28.3%	38.0%	20.5%	<**0.001**	>0.05	<0.01
8 to 9.9 s	40.0%	45.3%	38.6%	>0.05	>0.05	>0.05
6 to 7.9 s	19.1%	21.3%	25.0%	>0.05	>0.05	>0.05
4 to 5.9 s	25.7%	25.3%	43.2%	>0.05	<**0.001**	<***0.001***

Table 5: E-VOCs according to BMI

We investigated whether it is associated with other E-VOCS (Table 6).

	E-VOCs between 4 to 5.9s (170 patients)	No E-VOCs between 4 to 5.9s (515 patients)	P value
>97s	28.2%	39.4%	<0.001 inverted
89 to 97s	18.2%	19.8%	>0.05
75 to 89.9 s	19.4%	24.3%	>0.05
58 to 74.9 s	25.9%	30.5%	>0.05
42 to 57.9 s	35.9%	31.8%	>0.05
32 to 41.9 s	25.9%	24.1%	>0.05
18 to 31.9 s	27.6%	21.6%	<0.01
10 to 17.9 s	35.9%	27.8%	<0.01
8 to 9.9 s	47.6%	38.8%	<0.02
6 to 7.9 s	37.1%	14.4%	<0.001

Table 6: Other E-VOCs according to cluster 4 to 5.9s

Cluster 4 to 5.9s is inversely associated with cluster >97s and is associated with cluster 6 to 7.9s. See table 6. The pivotal E-VOCs belong to cluster 58 to 74.9s (Figure 3). E-VOCS could subsequently be split into two large sets: low molecular weight E-VOCs - rather associated with 4 to 5.9s and obesity – and high molecular weight E-VOCs – rather associated with tissue destruction, cancer, UC or vagal impairment.

We investigated which parameters are associated with cluster 4 to 5.9s (Table 7).

	E-VOCs between 4 to 5.9s (181 patients)	No E-VOCs between 4 to 5.9s (504 patients)	P value
Age	50.5 +/- 13.7	50.6 +/- 16.0	>0.05
BMI	23.3 +/- 4.4	23.1 +/- 4.3	>0.05
NLR	1.57 +/- 0.63	1.91 +/- 1.07	**<0.001**
LMW-HA (µg/l)	26.2 +/- 12.2	30.8 +/- 18.3	**<0.001**
Crohn	2.9%	5.2%	<0.01
COVID19 infection	4.7%	3.9%	>0.05
UC	6.5%	6.4%	>0.05
Eosinophil counts	192+/-160	176+/-152	>0.05
Glycaemia (µmol/l)	5.3 +/- 1.2	5.3 +/- 0.7	>0.05
All cancers or dysplasia	22.9%	25.4%	>0.05
Arrhythmia	7.7%	8.5%	>0.05
Decreased jejunal diameter	18.2%	18.0%	>0.05
Jejunal hypotonia	32.3%	35.2%	>0.05
Gastroparesis	6.5%	7.4%	>0.05

Table 7: Main clinical or biological parameters according to cluster 4 to 5.9s

Cluster 4 to 5.9s is not associated with jejunal spasm or hypotonia, severe inflammation (NLR is normal), or tissue destruction (LMW-HA levels are normal). A causal role of cluster 4 to 5.9s in the occurrence of obesity is highly unlikely. These E-VOCS should be considered as a simple marker of a specific biofilm.

We investigated which parameters are associated with cluster 10 to 17.9s (Table 8).
Cluster 10 to 17.9s characterizes a subgroup of patients with a high frequency of Crohn.

	E-VOCs between 10 to 17.9s (205 patients)	No E-VOCs between 10 to 17.9s (480 patients)	P value
Age	50.5 +/- 14.7	50.6 +/- 15.3	>0.05
BMI	23.4 +/- 4.1	23.0 +/- 4.4	>0.05
>97s	24.9%	41.7%	<0.001 Inverted
58 to 74.9 s	15.1%	35.6%	<0.001 Inverted
COVID19 infection	2.0%	5.2%	<0.001 Inverted
Crohn	8.7%	2.9%	<0.001
UC	5.4%	7.1%	<0.01 Inverted
NLR	1.78 +/- 1.0	1.84 +/- 1.0	>0.05
Glycaemia (µmol/l)	5.3 +/- 0.7	5.3 +/- 0.9	>0.05
LMW-HA (µg/l)	26.9 +/- 15.0	31.2 +/- 18.2	<0.01
All cancers or dysplasia	21.1%	33.8%	<0.01 Inverted
Arrhythmia	4.9%	9.8%	<0.001 Inverted

Table 8: Main clinical or biological parameters according to cluster 10 to 17.9s

Patients with Crohn are younger, which may explain less reported cancer/dysplasia, arrhythmia, osteoporosis or even depression (Table 9).

	Crohn's disease (32 patients)	No Crohn's disease (653 patients)	P value
Age	33.3 +/- 11.1	51.4 +/- 14.8	<0.001
BMI	22.0 +/- 2.8	23.2 +/- 4.4	<0.03
58 to 74.9 s **	6.3%	30.7%	<0.001
All cancer or dysplasia *	6.3%	15.0%	<0.001
Arrhythmia *	0%	8.7%	<0.001
Osteopenia*	0%	7.5%	<0.001
NLR	2.34 +/- 1.40	1.81 +/-0.96	<0.001
Depression	0%	12.1%	<0.001
LMW-HA (µg/l)	28.6 +/- 17.0	30.0 +/- 17.2	>0.05
Glycaemia (µmol/l)	5.3 +/- 0.6	5.3 +/- 0.8	>0.05
>97s	28.1%	37.1%	>0.05
8 to 9.9 s	46.9%	40.7%	>0.05
6 to 7.9 s	9.4%	20.5%	<0.01
4. to 5.9s	9.4%	27.0%	<0.001

* Cancer/dysplasia, arrhythmia, osteopenia are known to be age-dependant.
** Cluster 58-74.9s is known to be age-dependant and to be associated with cancer or arrhythmia.
Table 9: Relevant parameters according to Crohn's disease

Patients with Crohn exhale rarely E-VOCs of cluster 58 to 74.9s or of cluster 4 to 5.9s.

Cluster 10 to 17.9s is associated with Crohn or overweight. Table 10 shows that this cluster is rather associated with Crohn, not with overweight (Chi-square with Yates correction; $p<0.001$).

As a consequence, weight increase should at least be stratified within three sets: Crohn (rather with cluster 10 to 17.9s), obesity (rather with cluster 4 to 6.9s) or overweight not associated with Crohn (without a specific cluster).

	E-VOCs between 10 to 17.9s	No E-VOCs between 10 to 17.9s	Total number of overweight patients
Crohn	3 patients	1 patient	4
No Crohn	59 patients	87 patients	146
Total number of overweight patients	62	88	150

Table 10: Comparison of overweight patients (150 patients) with or without Crohn according to cluster 10 to 17.9s. Chi-square with Yates correction is used: $p<0.001$

We calculated the specificity of cluster 4 to 5.9s or of decreased jejunal diameter to distinguish between OB and OW groups.

The specificity (Sp) of cluster 4 to 5.9s is equal to 74.7% and the Predictive Positive Value (PPV) is 30.9%.

Sp of decreased jejunal diameter is equal to 17.3% only and the PPV is 25.7%.

However the association of both criteria enable to reach a Sp of 91.3% and a PPV of 56.7% (Table 11).

		Number of patients	OB group*	OW group**	Se§ Sp PPV NPV
Reduced jejunal diameter	**Yes**	167	43 (a)	124 (c)	97.7% 17.3% 25.7% 96.3%
	No	27	1 (b)	26 (d)	
Cluster 4 to 5.9s	**Yes**	55	17 (a)	38 (c)	38.6% 74.7% 30.9% 80.6%
	No	139	27 (b)	112 (d)	
Reduced jejunal diameter and cluster 4 to 4.9s	**Yes**	30	17 (a)	13 (c)	38.6% 91.3% 56.7% 83.5%
	No	164	27 (b)	137 (d)	

*No obese patient presented with Crohn or UC; ** respectively 4 and 5 patients of the OW group presented with Crohn or UC. None of them exhaled E-VOCs with cluster 4 to 6.9s

§ 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)

Table 11: Sensitivity (Se), Specificity (Sp), Positive predictive values (PPV), Negative predictive values (NPV) of cluster 4 to 5.9s or reduced jejunal diameter for OW group or OB group

Please note that no obese patient presented with Crohn or UC.

Respectively 4 and 5 patients of the OW group presented with Crohn or UC. None of them exhaled E-VOCs with cluster 4 to 5.9s.

Discussion

General overview

Overweight and obesity are characterized by increased adipose tissue mass and disturbed functions resulting in low-grade inflammation and development of T2DM and cardiovascular disease [41-43].

Overweight or obesity and E-VOCs including fatty acids: In mice, the cecum is a major site of small chain fatty acids SCFA [21] and the most abundant SCFA are acetate, propionate, and butyrate with an approximate molar ratio of 60:20:20, respectively [44-46].

In humans, after colonic absorption and transition to the systemic circulation, the molar ratio changes to approximately 91:5:4, respectively [47].

Gut-derived acetate production is expected to be low during states of low presence of fibres such as fasting. However, fasting-induced alterations in the gut microbiota may increase the *Firmicutes/Bacteroidetes* ratio and upregulate the pyruvate fermentation pathways leading to acetate and lactate production [48].

Human fasting and caloric restriction interventions increase microbial diversity with abundant acetate producers such as *Akkermansia Muciniphila (A. muciniphila)* [49,50].

In obese men and women, a positive association of fasting plasma acetate with the degree of adiposity was observed independent of age, sex, and ethnicity. Additionally, fasting plasma acetate levels correlated positively with de novo fasting hepatic lipogenesis [51].

Since the cluster 4 to 5.9s contains acetate, our epidemiological study confirms to link between obesity and exhaled acetate. However, the study rejected the association of acetate with overweight ($25 \leq BMI \leq 30$).

Lean patients rather exhale cluster 90 to 97s.

Pivotal values of E-VOCs can be estimated to locate at cluster 58 to 74.9s. Higher molecular weight VOCs could suggest dysbiosis associated with mucosal destruction and malabsorption, chronic inflammation with altered immunity, or vagal impairment.

Low-molecular-weight E-VOCs (below 57.9s) could suggest visceral fat synthesis and accumulation in liver, pancreas or mesentery root.

Crohn is also associated with visceral fat and peri-nodal inflammation especially in the mesentery root [52,53].
Crohn has been associated with specific E-VOCs [54-57] and with *Mycobacterium avium paratuberculosis* [58,59]. This bacteria may produce large amount of dimethylcyclopropane [60] which can stimulate macrophages through the MINCLE pathway [61]. Tiny amounts of essential oils may decrease the undesirable small gut bacterial burden and alleviate symptoms in Crohn [62] and therefore confirmed this bacterial hypothesis.

In this epidemiological study, Crohn was associated with cluster 10 to 17.9s, which is not a marker of overweight it-self. Crohn is never associated with obesity. Crohn does not favour T2DM.

Obesity and T2DM have recently been associated with omental fat infiltration and visceral or even blood translocation of *Enterobacteriaceae* [63-65].

We hypothesize that gut microbiota were different between Crohn and obesity. Both microbiota produce low molecular weight VOCs, translocate to fat and blood, and induce severe inflammation. However, the causative biofilms are mutually incompatible and produce specific and exclusive E-VOCs. These gases could enable to differentiate both diseases at very early stages.

On the contrary, biofilms producing high molecular weight VOCs could be associated with tissue destruction rather than fat production.

Overweight or obesity and tissue destruction or cancer/dysplasia: Overweight/obesity is associated with an increased risk of cancer [27-32].

However, in our study, the number of cancer/dysplasia was similar in the OW and OB groups and lower than in the lean group.

Since the study is retrospective, it appears logical that patients who developed cancer could have experienced weight loss due for example to chronic inflammation, adverse events related to long lasting treatments or loss of appetite.

Indirect parameters suggest chronic inflammation or tissue destruction in patients with overweight or obesity.

Neutrophil/lymphocyte ratio and eosinophil counts are considered to be reliable markers of immunity, especially in patients with colonic cancer [66-69].

As expected, NLR is correlated with BMI in our study. Obesity is associated with severe NLR increase and drop of eosinophil count. LMW-HA levels are within the normal range.

Overweight is associated with increased NLR and increased LMW-HA levels.

LMW-HA is known to increase endothelial permeability, stimulate receptors of cancerous stem cells and favour metastasis. Migration of stem-cells according to LMW-HA gradient has been documented [70-73].

An increase in LMW-HA levels may occur in case of NASH complicated with fibrosis [74,75]. However, no patient with such a complication was included in this observational study.

The number of patients with mild-COVID-19 and of IgG CMV+ was similar in the three groups. The frequency of herpetic flares was lower in the OB group.

Th1-immunosuppression is therefore probably not involved in the occurrence of overweight or obesity.

The lack of correlation between BMI and previous medical history of cancer may be explained by the young age of the observed population and the lack of immunosuppression.

The fact that the level of serum LMW-HA is increased in the OW group and that NLR correlated with BMI pinpoints the risk of these two populations to develop cancers later on.

It is noteworthy to mention that acetate is decreased in patients with dysplastic polyps or colorectal cancers [76]. In such patients, cluster 58 to 74.9s is expected to be elevated [23].

Overweight or obesity and parasympathetic activity: The vagal nerve is responsible of the parasympathetic tone of the digestive tract, from the pharynx to the splenic flexure of the colon (Cannon's point) [77].

Vagal afferent and efferent fibres interconnect the gut to the brain. They control immunity and inflammation of the gut [78-80].

A preliminary study performed on 254 patients who underwent transabdominal ultrasound examination to investigate vagal tonus identified two abnormal clinical pictures: hypotonia of the foregut (30.3% of the cases) with lack of gastro-duodenal voiding, jejunoduodenal reflux, enlarged jejunum with rare contractions and atrophic mucosa (less than 1 mm), and on the contrary hypertonia of the foregut (33.3%) with a decreased diameter of the jejunum (11.4 +/-3.0 versus 15.6 +/- 5.0 mm). This latter ultrasound picture was significantly associated with overweight, gastroesophageal reflux and ileal dilatation [81].

Obesity is associated with vagal hypertonia [82].

In support, neuromodulation of vagal tone has been tested for the treatment of metabolic diseases [83].

Promising results have been published with devices able to block under-diaphragmatic vagal tone [84-86].

Perry RJ *et al.* [87] described increased acetate levels and hyperparasympathetic activity in obese rats. However, we did not find any publication reporting such findings in humans. Overweight and obesity are frequently not stratified in publications, leading to contradictory results [88]; especially because overweight may be associated with vagal hypotonia and mucosal atrophy.

In our study, obesity is associated with cluster 4 to 5.9s (containing acetate) and with hyperparasympathetic (vagal) activity. However, a relationship between acetate and jejunal spasm is excluded.

We hypothesise that the jejunal biofilm which synthetize acetate hyper-stimulates the vagal nerve through another pathway than acetate production and without hindering the nerve or the mucosa.

In contrast, high molecular weight E-VOCs would rather generate mucosal atrophy and afterwards vagal hypotonia.

Consequently E-VOCs may be markers of mucosal or vagal impairments.

Arrhythmia and osteopenia: Heart rate variability (HRV) is a key parameter to measure vagal tone [36,37].

Decreased HRV is associated an increased risk of sudden death of cardiovascular origin, including arrhythmia [89,90], and of decreased survival in patients with cancer [91,92]. HRV is decreased in patients with depressive mood [93-95], gastroparesis [38] or osteopenia [96,97].

In our study, arrhythmias or osteopenia do not occur more frequently in patients of the OW or of the OB group.

Interestingly, arrhythmia is associated with cluster 58 to 74.9s, not with cluster 4 to 5.9s [23].

Vagal hypotonia could explain the occurrence of arrhythmia [98-100] as well as of gastroparesis [101,102]. Please note that vagal hypertonia (jejunal spasm) is frequently detected in OW patients (51.3%) and in OB patients (97.7%). Vagal hypertonia may explain the scarcity of arrhythmia or of osteopenia occurring in overweight/obese patients.

Depression: In our observational study, the percentage of depression in the OB group was high.
Depression has been reported in patients with dysbiosis, especially those producing methane [103-105]. However, controversies exist regarding the interest of methane measurement in exhaled breath [106,107]. In addition, results are contradictory. Microbiota diversity [108] and methane production is expected to be low in obese patients [109,110]. Furthermore, methane eradication by antibiotic therapy reduces the efficacy of bariatric surgery [111]. However, dysbiosis with methane and hydrogen production has also been associated with BMI increase [112,113]. As a consequence exhaled-methane is probably not a predictive marker of overweight/obesity.

Cluster 92 to 97s has been reported in depression [114]. This cluster is not associated with overweight or obesity.

Increased NLR has been associated with depression in diabetic patients [115], in female patients [116] or in patients with atopy [117]. NLR is associated with an increased risk of suicide [118].

Co-occurrence of obesity and mood disorders is well documented [119-122].

Chronic central-nervous-system inflammation may induced hypermethylation of specific genes and may consequently favour depressive mood [123]. The increase of cytokines such as LPS-induced IFNs has also been suggested [124].

Depression could therefore be explained by specific chronic visceral-fat-induced inflammation due to *Enterobacteriaceae*.

Interest of E-VOCS measurement and especially of X-PID 9500® use in patients with Overweight or obesity

X-PID 9500® may detects E-VOCs associated with depression (114), increased risk of mild COVID19 (24) or cancer/dysplasia (23).

This study focusses on cluster 4 to 5.9s for obesity.

High levels of acetone - which may belong to cluster 4 to 5.9s and which are correlated with glycaemia - have been reported in diabetic patients [125-129].

None of the included patients presented with type 1 *diabetes mellitus* or uncontrolled T2DM. Acetone was therefore not expected to skew the results of E-VOCs.

Although the specificity of cluster 4 to 5.9s is low (74.7%), the measurement of E-VOCs appears to be valuable in ambulatory gastroenterological practice, especially when ultrasound examination is performed concomitantly.

Cluster 10 to 17.9s was associated with overweight and with Crohn. This cluster may contain dimethylcyclopropane which could be produced by gut bacteria such as Mycobacterium avium paratuberculosis [60]. Further studies are ongoing to confirm that dimethylcycloprane belong to this cluster and to identify its specific retention time.

Interest of the association of ultrasound examination with E-VOCs measurement

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 [39,40] and should be more frequently used by gastroenterologists to control digestive motility, especially when vagal stimulation or inhibition by electric devices are planned.

The specificity of X-PID 9500® results, coupled with ultrasound examination findings, is high enough (91.3%) to plea for the use of these techniques on a routine basis. All the more so as X-pid 9500® helps to detect E-VOCs associated with other diseases within the same time.

Please note that ultrasound examination is routinely used for the follow-up of Crohn [130-133].
After the identification of fat and lymph nodes in the omentum by ultrasound examination, X-pid 9500® could differentiate between the two major biofilms which may induce such a radiological picture, within less than 1 minute.

Practical consequences to distinguish between overweight and obesity

Obesity is associated with vagal hypertonia and with acetate hyper production. However, acetate is not the primary cause of vagal hypertonia and therefore of obesity. It is only a marker of an inflammatory jejunal and mesenteric biofilm which should be modified. An early switch of the gut microbiota could enable to normalize vagal tone.

High fibres intake does not reduce acetate production [133] and butyrate increase does not improve, glucose and lipid metabolism [134].

In obesity, the richness of gut microbiota is poor [109]. The key point appears therefore to boost microbiota diversity with an increase in NO, H2S and methane production [135-138] rather than attempting to eliminate inappropriate faecal species such as *Enterobacteriaceae.*

The success of faecal transplantation in mice [139] or of bariatric surgery is mainly explained by the return to high microbiota diversity [140-142].

Repeated measurement of microbiota modification induced by diet, physical training, fecal/phage/bacteria transplantation, bariatric surgery – or any combination of these methods – may help to optimize the step by step process of acetate decrease and of NO/H2S increase.

When microbiota enrichment is successful, glycaemia, NLR and eosinophilic count (other markers of obesity) are expected to return within normal ranges. Since vagal nerve and mucosa are not altered, dramatic and quick modifications may be observed.

Overweight should be considered as a different disease with mucosal, vagal and perhaps myenteric alteration. The destruction of elastic tissues is objectified by high LMW-HA levels. Long lasting mild overweight should therefore trigger meticulous screening of cancer/dysplasia, and of neurodegenerative diseases. Adequate prevention, especially regarding deficiencies (due to mucosal atrophy) should be implemented.

The primary role of gut microbiota is less clear in overweight than in obesity. Vagal impairment associated with mucosal destruction and chronic inflammation is the possible first step. The role of specific oral bacteria which are known to participate to dysbiosis-associated cancers is possible [143-149].

E-VOCs measurements and ultrasound examination could enable to confirm vagal, mucosal and microbiome recovery. Since vagal nerve and mucosa are altered, slow and partial improvements are expected rather than quick and dramatic changes. LMW-HA levels should return within normal range.

Of course, early identification of Crohn will enable a rapid initiation of appropriate therapy.

Further studies are necessary to find which type of diet, physical recommendations and vagal stimulation are optimal for patients with overweight and without Crohn.

Conclusion

X-PID 9500 enables to detect specific E-VOCs associated with obesity: cluster 4 to 5.9s (probably acetate).

In obese patients transabdominal ultrasound examination found decreased diameter of the jejunum – attributed to vagal hypertonia – and preserved mucosa. Chronic inflammation due to a specific biofilm may explain a higher risk of depression.

In overweight patients, jejunal mucosal impairment with decreased jejunal motility associated with an increase in LMW-HA suggest tissue destruction.

Some patients with early Crohn may belong to the OW group. They rather exhale cluster 10 to 17.9s.`

Overweight (25≤BMI≤30) and obesity (BMI>30) appear to be two different diseases and not a simple continuum.

X-PID 9500®, especially when associated with transabdominal ultrasound, is a precious ambulatory tool to optimize prevention and attempts to enrich the gut microbiota.

Acknowledgments and Conflicts Of Interest

No conflict of interest to disclose.

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