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Weight Loss Associated with Maitake Or Tiny Amounts of Essential Oils

(Running title: Weight loss associated with maitake)

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Abstract

Background: *Maitake or essential oils intake has been associated with weight loss.*
Objective: *Assess whether maitake or tiny amounts of essential oils (EO) may favour weight loss. Specify the mechanisms of action: modification of microbiota, clearance of liver steatosis, increased gastric voiding, decreased jejunal spasm or improvement of jejunal hypotonia.*
Methods: *Descriptive retrospective epidemiological study with data collected during routine gastroenterological consultations in patients with small intestinal bacteria overgrowth.*
Results: *206 patients are included: 37 with obesity, 76 with overweight and 93 with normal weight.*
In obese/overweight patients, maitake, EO or maitake+EO favours weight loss: respectively -8.2 kg +/-5.9 versus 0.5+/-5.2; -6.2 +/- 7.3 versus 0.5+/-5.2 and -6.9 +/- 6.6 versus 1.4+/-5.3 ($p<0.001$). Maitake releases jejunal spasm whereas EO does not. Maitake or EO decreases liver steatosis. Jejunal hypotonia remains uncontrolled.
No synergy with maitake + EO was observed except in patients with normal weight for whom it enables drastic recovery of jejunal hypotonia. In this group maitake, EO or maitake+EO also favours weight loss.
Conclusion: *Maitake or EO may help to decrease body weight. The association Maitake+EO may help normal weight patients with visceral fat to lose weight and recover vagal tone. The mechanisms of action, yet hypothetical, are discussed.*

Keywords: *maitake-essential oils-weight loss-liver steatosis-jejunal hypotonia.*

List of abbreviations

BMI: Body Mass Index; **COVID-19:** Coronavirus Disease; **CZM:** Citrus lemon+Zingiber officinale+Melaleuca alternifolia; **EO:** essential oils; **E-VOCs:** Exhaled Volatile Organic Compounds; **FODMAPs:** fermentable oligosaccharides disaccharides monosaccharides and polyols; **H2S:** Hydrogen sulphide; **IBS:** Irritable bowel syndrome; **LMW-HA:** Low molecular weight hyaluronic acid; **NLR:** Neutrophil lymphocyte ratio; **NO:** Nitric oxide ; **NW:** Normal weight; **O/O:** Obesity or overweight ; **SCFA:** Small chain fatty acids; **SIBO:** Small Intestinal Bacterial Overgrowth; **T2DM:** Type 2 *Diabetes mellitus*; **TLR-4:** Toll-like-receptor-4.

Introduction

Obesity or overweight (O/O) have reached pandemic proportions [1] and spread now to younger populations, especially in low- and middle-income countries [2]. There is a growing consensus that visceral obesity represents an important risk factor for diabetes, cardiovascular diseases and different types of cancer [3-11]. Recently, obesity has also been recognized as major risk factor for coronavirus disease-19 (COVID-19)-related prognosis [12-21]. Therefore, prevention of O/O becomes crucial, regardless of age.

Causes of O/O seem to be getting in place early in life and lead to chronic inflammation and sequelea. It is therefore particularly difficult to switch back from O/O to normal weight (NW) in adults, suggesting that O/O should rather be considered as a complication than an initial condition.

O/O could be two separate diseases with different causes [22]. Obesity is rather associated with jejunal spasm (vagal hypertonia and acetate hyperproduction), liver steatosis and non-alcoholic liver steatosis, whereas overweight is associated with mucosal and vagal impairment (jejunal

hypotonia) [22, 23]. However, they are both associated with dysbiosis and vagal impairement.

Type 2 *Diabetes mellitus* (T2DM), which is a recognized complication of O/O, is also associated with gastroduodenal voiding disturbances possibly due to alteration of vagal tone or of myenteric plexus activity [24, 25].

Ultrasound examination and breath testing, especially with measurement of exhaled volatile organic compounds (E-VOCs) or of nitric oxide (NO)/ hydrogen sulphide (H2S) [22, 23, 26, 27] may help to identify voiding disturbances and microbiota alterations.

They also may identify patients with spurious NW, however presenting with increased visceral fat and sarcopenia. Many factors have been implicated in the occurrence of O/O, especially inappropriate diet and sedentarity. However, altered microbiota appears to be another major factor [28-33].

When given early in life, antibiotic therapy may disrupt microbiota composition, and its metabolic activity. It may affect the body mass of the host by either promoting weight gain or stunting growth [34-37].

Although O/O-related microbiota disturbances could be repaired either by the transfer of bacteriophages [38] or by bariatric surgery [39], we should look for more natural, less dangerous and less expensive methods.

Dietetic advices

Decreased fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAPs)

The most complained gastrointestinal symptoms in small intestinal bacteria overgrowth (SIBO) are similar to those in irritable bowel syndrome (IBS), i.e. chronic diarrhoea, bloating and abdominal pain. Once malignancies and inflammatory bowel diseases are excluded, the so called "IBS-like disorders" should be taken into account.
IBS disorders entangle FODMAPs, lactose, non-celiac gluten sensitivity or nickel intolerance and are all associated with dysbiosis and SIBO [40-42].

Since all included patients presented with SIBO, they were all recommended a low-FODMAPs diet.

Decreased energy dense food

Consuming energy-dense food, like confectionaries, sugars, soft drinks, fats, and alcohol are highly correlated with obesity and chronic diseases [43-45]. Patients were asked to give up such highly caloric foods. Cereals, beans, peas, soy beans and lentils are already diminished in low-FODMAPs diets.

Decreased nickel

Nickel allergy is associated with O/O [46-50]. Beneficial effects of low-nickel diet have been confirmed in IBS-like syndromes [51].

Nickel induces inflammation by stimulating macrophage through Toll-like-receptor-4 (TLR-4) activation. Blockade of TLR-4 signalling completely inhibits the nickel-induced activation [52]. Specific oral bacteria are required for the occurrence of nickel-intolerance [53].

Our dietetic recommendations for patients with O/O or with visceral fat at ultrasound examination

In addition to low nickel intake [54], we suggest low FODMAPs diet (since all patients present with SIBO) as well as sugars, soft drinks, fats, and alcohol restrictions.

Patients were therefore asked to avoid whole wheat or oats, multigrain bread/cereals/pasta, canned food, beans, lentils, peas, soy beans, kale and spinach, shellfish and herring, pineapple, chocolate milk and food complements containing nickel. Blanching of vegetables was suggested to decrease the amount of heavy metals.

With such a diet, lactose, gluten, nickel and FODMAPs intake was low. Caloric content was fairly reduced without a decreased intake of vegetables, unsaturated fatty acids or assimilable proteins.

Reduction of gluten-intake is also associated with mild weight loss [55, 56]. A low-FODMAPs diet complies with substantial decrease in gluten.

Maitake

Maitake (*Grifola frondosa*) has been associated with weight loss in humans [57, 58] and with the control of metabolic syndrome in animal models, especially due to the regulation of gut microbiota [59-61].

Maitake is an immunostimulating agent [62] with anti-viral effects [63], including enterovirus 71 (foot-hand-mouth disease) [64]. This latter virus has recently been implicated in the occurrence of celiac disease [65, 66], a well-known condition associated with mucosal duodeno-jejunal atrophy.

Maitake stimulates macrophages through the TLR-4 pathway, in synergy with water-soluble agonists derived from gut colonizing bacteria [67-69]. This mechanism is similar to the one described with nickel-intolerance (see above). However, non-conserved histidines 456 and 458 of human TLR-4 are required for activation by Ni (2+). On the contrary, natural ligand lipopolysaccharides (like maitake) do not requires mutations and exert a direct physiological activation [70].

Adenovirus 36 may induce O/O [71-73]. In general, all adenoviruses modulate TLR-4 signalling to facilitate their intracellular transport [74] and nickel favours their entry into endothelial cells [75].

Adenoviruses frequently contaminate soils, berries and vegetables, especially in cases of soil contamination by nickel [76-79]. Blanching could become an advantage.

Polyphenols seem to be good anti-adenoviruses agents [80-82], especially because they down-regulate TLR-4 signalling [83-85].

Because of it action on TLR-4, maitake may exert a blockade of adenovirus entry or may decrease adenovirus-induced chronic inflammation.

Essential oils

Essential oil (EO) of *Citrus lemon* may reduce jejunal spasm and stimulate intestinal transit rate [86]. In addition, it depolarizes the pacemaker potentials in murine small intestinal interstitial cells of Cajal, enabling peristalsis [87].

EO of *Zingiber officinale* contains potent anti-inflammatory, antidiabetic, antilipolytic compounds which may regulate jejunal activity [88-90].

EO of Melanoleuca angustifolia showed a potent bactericidal activity against *Acinetobacter baumanni* [91] which is one of the most important nosocomial opportunistic pathogens worldwide. Obesity has been associated with an increased risk of nosocomial infection, suggesting that there may be an association between *A. baumannii* and white adipose tissue. Exposure to *A. baumannii*-derived lipopolysaccharides was found to increase the expression of several adipokines in adipocytes and significantly reduced the expression of leptin and adiponectin [92].

Essential oils have not inhibitory effects on adenoviruses [93, 94]. In our practice, a mixture of *Citrus lemon + Zingiber Officinale + Melaleuca alternifolia* (CZM) was suggested to the patients.

Objectives of the study

We investigated whether maitake and/or tiny amounts of essential oils could induce weight loss and whether they influence E-VOCs, gastric or jejunal voiding and recovery of liver steatosis.

This investigation concerns usual practice and takes compliance into account. It also includes NW patients since some of them present with sarcopenia, increased visceral fat, jejunal hypotonia and liver steatosis. If these patients had a normal muscle mass, the diagnosis would have been overweight.

We collected data regarding 1) Body weight, diet and diet compliance, 2) maitake intake, essential oils intake and compliance, 3) gastric emptying and jejunal spasm, jejunal hypotonia, or liver steatosis. We took advantage of the ultrasound examination which is routinely performed when SIBO to investigate liver steatosis as well as gastric, jejunal and ileal movements [23, 95].

Compliance is a main stumbling-block in long term therapy, especially regarding prevention and without the sting of symptoms reduction. We therefore routinely measure compliance with the Morisky questionnaire [96] and by controlling of the ordering forms [97, 98] of maitake or CZM.

Material and methods

This work is a descriptive retrospective epidemiological study. Data were collected during the normal course of routine gastroenterological consultations for SIBO. The recruitment started on 2015 January 1st and the last follow-up consultation ended on 2021 February 1st. 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 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 included patients consulted for SIBO and underwent a breath test. The first consultation started between 2015 January 1st and 2020 February 1st. The last follow-up consultation was planned on 2021 February 1st. The follow-up period lasts at least one year. Patients are followed every 6 months.

Patients should provide with a full medical history, especially regarding diet, medication intake (especially hormones), and thyroid status. A transabdominal plus thyroid ultrasound examination is routinely performed in patients consulting for SIBO. Patients underwent a breath test after a fasting period of at least 12 hours. All patients should have discontinued antibiotic therapy for at least 3 weeks before coming to the consultation for SIBO in order to avoid altered digestive flora. Detailed results of gas measurement are not provided in the study since SIBO is not targeted. Only fasting levels of E-VOCs will be provided. Patients signed a written consent for the possible retrospective use of the epidemiological collected data.

Exclusion criteria: Uncontrolled Crohn, ulcerative colitis, auto-immune hepatitis, rheumatoid arthritis, multiple sclerosis, sarcoidosis, uncontrolled endocrine disease (including thyroid insufficiency or *diabetes mellitus*), mastocytose or mast cell activation syndrome, anorexia, pancreatitis or HIV infection. Lack of transabdominal ultrasound, signed consent for possible retrospective epidemiological use of data. Recent or repeated massive destruction of the digestive flora by antibiotic therapy or oral intake of essential oils leading to and less than 2 ppm of E-VOCs at the first measure, after 10 hours of fasting. Incomplete data on drug or food complement intake.
Body mass index (BMI) below 18.5.

Gas measurement: The patient comes after at least 12 hours of fasting. He/she exhales the air of the lungs in a neutral plastic bag (Contralco®; Gignac; France; www.contralco.com).

Nitric oxide (NO) and hydrogen sulphide (H2S) were measured by the X-am8000®, an ambulatory device associated with photoionization detection technology [Dräger; Lubeck; Germany; www.draeger.com › Products ›

Multi-Gas-Detectors]. X-am8000® detects NO or H2S concentrations as low as 0.1 particle per million (ppm).

The device is portable and equipped with a powerful pump. Patients could be placed in separate rooms when necessary. The setup is basic and only requires a short neutral tube to connect the bag and the device.

Ultrasound

Lack of gastroduodenal 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 could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is visualized. Jejunal spasm was diagnosed when the opening between the superior mesenteric artery and the aorta was less than 5 mm and when the first and the second jejunal loops measure less than 15 mm despite osteopathic manoeuvers [23, 95]. Abdominal ultrasound examination also enables to diagnose liver steatosis.

Diet restriction

Low-FODMAPs diet was suggested to all patients since they all present with SIBO. Dietetic restrictions (exclusion of sugars, soft drinks, fats, and alcohol) as well as low nickel intake were recommended to patients with O/O, liver steatosis or visceral fat at ultrasound examination, even in NW patients.

Food mushrooms

Maitake was recommended (200 mg twice a day in food or on the tongue) on a long-term basis. Maitake possesses immunostimulating properties [62] and may modify gut-TH1 immunity [63]. Although an impact of gut-TH1 immunity on weight loss is unlikely, a control group with Ganoderma lucidum – which also possesses such properties [99] - was introduced as a control group.

Essential oils

Because of their potent anti-inflammatory, antidiabetic, antilipolytic, antispasmodic, prokinetic or antibacterial effect, tiny amounts of essential oil of Citrus lemon, Zingiber Officinale or Melaleuca alternifolia were given every day according to a protocol which has been described elsewhere [100]. In summary, a mixture of Laetiporus sulphureus (mycelia grown on barks; 200 mg/dose) + EO of Citrus lemon (1/30 of drop per dose) + EO of Zingiber officinale (1/40 of drop per dose) + EO of Melaleuca alternifolia (1/40 drop per dose) [CZM] was recommended: One dose per day orally in food or on the tongue, in the morning.

The mycelium of *Laetiporus sulphurous* possesses anti-inflammatory and antifungal plus anti antibacterial properties [101-105]. In addition, *Laetiporus sulphurous* contains eburicoic acid with protects gastric mucosa [106].

Control group

All consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria were identified. As a consequence, no recruitment or selection bias is expected.

The control group was the group not treated or not-compliant regarding mushrooms intake, essential oils intake or diet recommendations. Since patients were split into two groups (O/O or NW patients), two control groups have been defined.

Compliance

The compliance was evaluated by two methods. Firstly, the patient fills the Morisky's questionnaire [96]. The compliance was assessed acceptable when the score exceeds "6". Secondly, compliance was evaluated according to the copies of all ordering forms of maitake or of CZM. We requested at inclusion and we remind this requirement at the end of every following consultation that the patient should provide a copy of each ordering form to the clinical centre [97, 98].

Statistics

Comparisons of percentage used two-sample t-tests. Yates correction was used for small samples. Comparisons of means used a Student's t-test. Groups were compared for all parameters. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p<0.01$.

Results

This descriptive epidemiological study includes 206 patients: 37 with obesity, 76 patients with overweight and 93 patients with NW.

Patients with obesity present more frequently with non-alcoholic steatohepatitis. Although jejunal hypotonia appears to be more frequent in patients with overweight (trend, $p<0.02$), we considered that the data of the groups obesity and overweight could be merged.

Patients with NW (and SIBO) present with less jejunal spasm and liver steatosis or non-alcoholic steatohepatitis than those with O/O. They also present more frequently with jejunal hypotonia than obese patients (68.8% versus 27.0%; $p<0.001$). Please note, that jejunal spasm and jejunal hypotonia are not compatible.

Glycaemia was also lower in the group NW. The mean duration of follow-up is equal to 2.0 +/- 1.3 years for patients with O/O and 1.9 years +/- 1.2 for NW. The descriptive demographic data are summarized in (table 1).

	Obesity (BMI>30) 37 patients	Overweight (25≤BMI≤3) 76 patients	Obesity versus overweight P values	Normal (18.5≤BMI<25) 93 patients	Obesity versus normal P values	Overweight versus normal P values
Age (years of age)	53.9 +/- 13.7	54.5 +/- 0.72	>0.05	51.5 +/-12.7	>0.05	>0.05
Female patients	70.3%	56.6%	>0.05	72%	>0.05	>0.05
Gastric emptying	10.8%	13.2%	>0.05	12.9%	>0.05	>0.05
Jejunal spasm	70.3%	50.0%	>0.05	18.3%	<0.001	<0.001
Jejunal hypotonia	27.0%	47.4%	<0.02	68.8%	<0.001	<0.02
Liver steatosis	94.6%	84.2%	>0.05	34.4%	<0.001	<0.001
Non-alcoholic steatohepatitis	37.8%	15.8%	<0.001	2.2%	<0.001	<0.001
Glycaemia (µmoles/l)	6.3 +/- 1.6	5.8 +/- 0.1	>0.05	5.2+/-0.6	<0.001	<0.001
E-VOCs in breath (ppm)	4.7 +/- 3.7	5.5 +/- 0.1	>0.05	8.0+/-6.8	<0.001	<0.001

Table 1: Demographic data at inclusion according to BMI.

Weight loss in patients with O/O

Patients who did not take any food complement and who did not comply with dietetic recommendations (control group) experienced weight increase (approximately 2.5 kg, trend with p value <0.05) in comparison with the group following dietetic advices).

Ganoderma lucidum intake did not induce any weight loss with suggest not effect of gut-TH1 stimulation.

Maitake, CZM or maitake+CZM enables weight loss: respectively -8.2 kg +/-5.9, -6.2 +/- 7.3 and -6.9 +/- 6.6 (p<0.001).

Maitake releases jejunal spasm whereas CZM did not. CZM improves jejunal hypotonia whereas maitake did not. Maitake, CZM or Maitake+CZM improve gastric emptying or liver steatosis. No synergy has been triggered by the combination of maitake+CZM. Glycaemia remains unchanged. (See table 2).

	Control group 30 patients	Maitake intake (without CZM or Ganoderma) 29 patients	CGAT intake (without maitake or Ganoderma) 16 patients	Ganoderma intake (without maïtaké or CZM) 4 patients	Maitake+CZM intake (without Ganoderma) 33 patients	Compliance to dietetic recommendations (without maïtaké, CZM or Ganoderma) 18 patients
Recovery of gastric emptying	0%	13.7% p<0.001	18.7% p<0.001	0% Not applicable	12.1% p<0.001	5.6% Not applicable
Recovery from jejunal hypotonia	10%	13.8% p>0.05	43.8% p<0.01	25.0% p<0.02	12.9% p>0.05	5.5% p>0.05
Recovery from jejunal spasm	10%	27.6% p<0.01	18.8% p<0.02	25.0% p<0.02	22.6% p<0.04	11.1% p>0.05
Recovery from liver steatosis	10%	34.5% p<0.01	31.3% p<0.01	25.0% p<0.02	30.3% p<0.001	16.7% p>0.05
Variation of body weight (in kg)	2.5 +/- 4.6	-8.2 +/- 5.9 p<0.001	-6.2 +/- 7.3 p<0.001	-2.0 +/-3.5 p<0.04	-6.9 +/- 6.0 p<0.001	-0.2 +/- 5.1 p<0.05
Variation of E-VOCs	0.0 +/- 5.2	2.5 +/- 7.8 p>0.05	0.9 +/- 7.4 p>0.05	1.2 +/- 0.9 p>0.05	3.3 +/- 5.8 p<0.02	1.9 +/- 3.4 p>0.05
Variation of glycaemia	0.4 +/- 0.9	0.4 +/- 1.7 p>0.05	0.3 +/- 0.6 p>0.05	0.1 +/- 0.6 p>0.05	0.2 +/- 0.5 p>0.05	0.3 +/- 1.5 p>0.05

Table 2: Follow-up (mean=2.0 years +/-1.3; within 1 to 6 years) of patients with O/O according to recommendations. The control group includes patients who did not take maitake, CZM or Ganoderma lucidum. 86.7% of patients of the control group were not compliant. P values are calculated in comparison with the control group. Calculation of p value was not applicable when the number of cases was very low.

Weight loss in NW patients

Patients who did not take any food complement and who did not comply with dietetic recommendations experienced weight increase (approximately 1.04 kg, not statistically significant, possibly due to the lack of power).

Although compliance with dietetic recommendations appears to improve gastric emptying, it did not lead to weight loss. Release of jejunal spasm, recovery of jejunal hypotonia or decrease in liver steatosis appears to be key factors for weight control.

Jejunal hypotonia is particularly improved by the association Maitake+CZM (71.4% versus 17.8%, p<0.001), which was not observed in the group O/O. The higher severity of jejunal hypotonia in this latter group may explain this difference. Maitake, CZM or maitake+CZM intake is associated with weight loss: respectively -0.9 +/- 2.5, -2.5 +/- 1.2, -2.1 +/- 1.1 (p<0.01 to p<0.001).

Maitake or maitake+CZM improved gastric emptying. Maitake, CZM or maitake+CZM decreases liver steatosis. Maitake or CZM alleviate jejunal spasm. Glycaemia remains unchanged. (See table 3).

	Control group 45 patients	Maitake intake (without CZM or Ganoderma) 13 patients	CGAT intake (without maitake or Ganoderma) 16 patients	Ganoderma intake (without maitake or CZM) 31 patients	Maitake+CZM intake (without Ganoderma) 7 patients	Compliance to dietetic recommendations (without maitake, CZM or Ganoderma) 43 patients
Recovery of gastric emptying	6.7%	16.1% p<0.001	12.5% p<0.02	9.1% p>0.05	14.3% p<0.01	20.9% p<0.001
Recovery from jejunal hypotonia	17.8%	18.2% p>0.05	25.0% p>0.05	16.1% p>0.05	71.4% p<0.001	24.7% p>0.05
Recovery from jejunal spasm	2.2%	18.1 p<0.001	12.5% p<0.001	0% Not applicable	0% Not applicable	0% Not applicable
Recovery from liver steatosis	8.9%	36.4% p<0.001	18.8% p<0.01	6.5% p<0.05	28.6% p<0.01	11.6% p>0.05
Variation of body weight (in kg)	1.04 +/- 3.5	-0.9 +/- 2.5 p<0.001	-2.5 +/- 4.6 p<0.001	1.4 +/- 4.0 p>0.05	-2.1 +/- 2.6 p<0.01	0.8 +/- 3.0 p>0.05
Variation of E-VOCs	-1.2 +/- 9.6	5.0 +/- 5.4 p<0.001	1.0 +/- 6.4 p>0.05	-1.5 +/- 6.2 p>0.05	3.7 +/- 2.9 p<0.01	-1.2 +/- 7.3 p>0.05
Variation of glycaemia	0.4 +/- 0.7	0.4 +/- 0.6 p>0.05	0.1 +/- 0.5 p>0.05	0.2 +/- 0.5 p>0.05	0.4 +/- 0.5 p>0.05	0.2 +/- 0.6 p>0.05

Table 3: Follow-up (mean=1.9 year+/-1.2; within 1 to 6 years) of patients with NW according to recommendations. The control group includes patients who did not take maitake, CZM or Ganoderma lucidum. 55.7% of patients of the control group were not compliant. P values are calculated in comparison with the control group. Calculation of p value was not applicable when the number of cases was very low.

VOCs

VOCs level was higher in NW patients who are expected to present with a higher microbial diversity. In NW, VOCs increases when weight decreases (especially in those who took maitake or maitake +CZM). No increase was observed in patients who ingested CZM only. Maitake may increases microbiota diversity whereas CZM may decrease it. In patients with O/O, VOCs increase was not observed. However, a trend is noted in the group receiving maitake+CZM. It is possible that the severity of the alteration of the microbiota may hinder the recovery of diversity.

Discussion

Comprehensive view

Early prevention of O/O becomes crucial [1]. It should start early to avoid chronically altered microbiota leading to definitive chronic low-grade inflammation and sequelae jejunal hypotonia or vagal disturbances. In this epidemiological study, children were not included.

Patients with O/O present with hyperglycaemia. Chronic inflammation, destruction of mucosa, vagal impairment, and decreased immunity are well documented complications of T2DM [28, 29, 107, 108].

Despite clinically relevant weight loss associated with maitake and/or CZM, glycaemia remained unchanged as well as jejunal hypotonia in the O/O group-except partially for the CZM group. These facts suggest cureless chronic inflammation.

In the NW group who receives maitake+CZM, weight loss was associated with a drastic recovery of jejunal hypotonia. Jejunal recovery could be considered as a return to the normal condition with normal vagal tonus and peristalsis. When followed by patients with NW, dietetic recommendations were associated with a moderate rate of jejunal recovery, despite the lack of weight loss.

We suggest that jejunal impairment can be reversible only in NW patients. A loss in visceral fat – even at a higher level - is not sufficient in O/O patients.

Mucosal or submucosal inflammation could be the initial trigger of vagal impairment, leading to stagnation of food in the jejunum, SIBO, excess in fatty acids synthesis, visceral fat accumulation and finally a second wave of inflammation in the viscera involved by steatosis (pancreas, liver, mesentery root, etc.).

Should this hypothesis be confirmed, prevention should start as soon as jejunal hypotonia occurs, before visceral fat accumulation and well in advance of the second wave of dysbiosis which is more likely associated with different types of bacteria.

In NW patients, dietetic recommendations associated with maitake+CZM appears to be particularly efficacious. It is likely that some NW patients present with sarcopenia and increased visceral fat. They eventually benefit from mild to moderate weight loss.

Dietetic advices

Dietary habit is a major determinant factor for health, not merely to obesity [1]. Meta-analyses concerning intermittent energy restriction - which encompasses dietary approaches including intermittent fasting, alternate day fasting, and fasting for two days per week - showed that intermittent energy restriction was more effective than no treatment for weight loss (-4.14 kg) and achieved similar changes in body weight in comparison to continuous energy restriction [109, 110].

Low-carbohydrate diets are increasingly used to help patients with obesity and T2DM. Adopting a low-carbohydrate diet is a legitimate and potentially effective treatment option for patients with diabetes or obesity [111-113].

In this epidemiological study, compliance with dietetic recommendations did not lead to weight loss at the end of the follow-up period for patients with O/O. Recovery of gastric voiding, of jejunal hypotonia or of jejunal spasm was not observed. VOCs level in breath was not modified. Therefore, FODMAPs reduction, nickel eviction, low-carbohydrate/sugar/alcohol intake did not significantly modify results.

In patients with NW, compliance with dietetic recommendations enables a better gastric voiding in comparison with non-compliant patients. However, diet is helpless in patients with O/O.

Dietetic recommendations do not appear to increase VOCs levels and therefore do not strikingly improve the microbiota.
Dietetic observance did not remove visceral fat from the liver.

As a consequence, although the impact of dietetic recommendations and exercise on weight loss is undebated, their effect on long-term weight loss is clinically insufficient. They apparently do not tackle the root causes or corrective action is taken too late.

Maitake and weight loss

Maitake is helpful in controlling metabolic syndrome and increasing microbiota diversity (57-61). In this epidemiological study, maitake induces significant weight loss with improvement of jejunal spasm and of liver steatosis in both O/O or NW patients. Increased VOCs levels were only observed in patients with NW.

However, maitake did not improve jejunal hypotonia. These findings are consistent with the above-mentioned publications.

Decreased jejunal spasm could be attributed to decreased small chain fatty acid (SCFA) production [114] or to decreased inflammation. Suppression of TNF-alpha production has been reported with maitake [115].

Since no effect has been observed in the group with *Ganoderma lucidum* we can exclude a key role of TH1 immunity, modification of microbiota or reduction of accumulation of fat in the liver. Indeed, *Ganoderma lucidum* is also able to increase microbiota diversity [116] and is a well-documented immunostimulating agent [99]. *Ganoderma lucidum* is also considered as a performant hepatoprotective agent [117] and reduces the accumulation of fatty acids in the liver [118]. In addition, *Ganoderma lucidum* increases butyrate and triggers the gut Bacteroides-folate-liver pathway [119, 120].

It is noteworthy that some food-associated mycotoxins alter jejunal mucosa and the gut microbiota and may induce a leaky gut syndrome [121, 122]. *Coriolus versicolor* protects the jejunal mucosa against mycotoxins [123]. *Ganoderma lucidum* has no effect against mycotoxins, although its spores may have some anti-mycotoxins properties [124].

An effect of maitake against mycotoxins has never been reported.

Maitake possesses immunostimulating properties [62] and may, like other mushrooms (*Coriolus versicolor*, *Ganoderma lucidum* or *Phellinus linteus*) decrease viral infection [63].

Adenovirus 36 has been associated with obesity [71-73]. A role of TLR-4 and nickel is essential to induce chronic inflammation and perhaps jejunal disturbances. Maitake could bind to TLR-4 in such a way that it may antagonize severe activation and only enable mild physiological stimulation [68-70].

The effect of maitake is therefore genuine and overpasses other mushrooms regarding weight loss and liver steatosis recovery. This effect cannot be explained by the stimulation of immunity, by anti- mycotoxin properties, by a simple modification of SCFA production leading to alleviation of liver steatosis or by a direct anti-adenovirus effect.

Maitake does not repair jejunal hypotonia, even in patients with NW. Such an effect requires the association with CZM and is mainly observed in patients with NW.

CZM may modify oral microbiota. Some oral bacteria are known to be required to synergize maitake effect [69]. On the contrary, other bacteria may favour Ni (2+) activation of TLR-4 and trigger adenovirus 36 infection [70].

We therefore suggest that viral infections are probably not the direct cause of disturbed motility and altered mucosal wall. Severe local jejunal inflammation should rather be considered. The anti-inflammatory properties of maitake may therefore be the most relevant explanation of its effect.

Despite several publications reporting hypoglycaemic properties of maitake [125, 126], this epidemiological study does not confirm any glycaemia decrease.

The beneficial role of maitake on liver steatosis may be explained by the modification of cecal microbiota, of the SCFA synthesis and of the secretion of biliary salts [114,126].

Essential oils and weight loss

EO of *Citrus lemon* may reduce jejunal spasm and stimulate intestinal transit rate [86, 87]. EO of *Zingiber officinale* also contains potent anti-inflammatory, antidiabetic, antilipolytic which may regulate jejunal activity [88-90].
EO of *Melanoleuca angustifolia (EOMA) showed a potent bactericidal activity against Acinetobacter baumanni* [91] which may be implicated in reduced expression of leptin and adiponectin [92].

Studies have documented the benefits of EO on the growth performance of poultry and swine, especially of *Melaleuca alternifolia* [127-130]. Supplementation of broilers by EO of *Melaleuca alternifolia* improves cecal microflora composition, immunity (increased relative weight of spleen and thymus), and antioxidant capacity in the jejunum and ileum [131, 132].

Possible mechanisms of action of CMZ

In this epidemiological study, CZM alone induces weight loss, favours gastric emptying, and alleviate jejunal hypotonia or liver steatosis in O/O. In this group, CZM intake did not influence E-VOCs levels.

The effect of CZM was also observed in patients with NW, especially regarding weight loss, jejunal spasm or liver steatosis.

CZM appears to control jejunal hypotonia in O/O, whereas it controls jejunal spasm in NW patients. We hypothesized that CZM decreases jejunal spasm when is not associated with vagal impairment. In O/O, gastric bacteria may synthetize large amounts of acetate leading to permanent inflammation or fibrosis. CZM may decrease local bacteria and trigger gastric pacemakers and voiding. However, jejunal spasm remains uncontrolled.

Lack of synergy between maitake and CZM

In O/O patients, no clear synergy was observed with the association maitake + CZM. The association did not lead to any further weight loss. No further increase in E-VOCs levels or no effect on jejunal hypotonia was observed.

Interestingly, in patients with NW, maitake+CZM drastically improve jejunal hypotonia. This may suggest vagal tone recovery and has never been reported before.

Maitake+CZM could be the appropriate recommendation for the early prevention of O/O in young adults. The mechanism of action has still to be specified and the benefit of the association maitake+CZM versus maitake alone or CZM alone has to be further documented. We hypothesize that maitake could decrease chronic inflammation in the foregut/liver when CZM could release jejunal spasm and trigger Cajal-dependant pace-maker activity of the stomach and of the jejunum.

Limitations of the study

It is a retrospective epidemiological study with a large diversity of therapies and behaviours. However, except body weight and its possible direct causes or consequences, the population included was quite homogeneous because of restrictive inclusion and exclusion criteria. Compliant and non-compliant groups regarding dietetic recommendations were similar according to demographic data, E-VOCs or digestive vagal alterations, and there is no reason to suspect any interfering factor.

However, two biases can be evoked. Firstly, dissatisfaction may be correlated with lack of observance and may end to patients lost to follow-up. Since no side effects are associated with the intake of low amounts of mushroom or of CZM, only dissatisfaction with effectiveness can be evoked. Such a bias will reduce the percentage of failure in the non-compliant group and will decrease the difference between the two groups.

Secondly, some patients of the non-compliant group may have partially taken CZM. Such a situation will also decrease the difference between the two groups.

In both instances, the biases tend to misleadingly narrow the differences between the two groups. It therefore suggests an even stronger effect of maitake and/or CZM and consequently does not invalidate the findings.

Exercise and sedentary lifestyle were not taken into consideration. It is probable that non-compliant patients are similar to those who do not apply dietetic recommendations. This will skew the repartition of sedentary patients in control groups. However, the impact of physical activity on long-term weight loss maintenance is debatable when monthly counselling is not implemented [140].

In addition, there is no argument to support any unbalance between groups receiving maitake, CZM or maitake+CZM regarding physical activity.

Application of this new knowledge for routine practice

Long term intake of small doses of maitake or of CZM may help to decrease body weight in O/O patients as well as chronic inflammation of the foregut.

Maitake+CZM can be even more beneficial in patients with NW. It may help to recover from jejunal hypotonia and therefore from initial transient vagal alteration.

The mechanism of action possibly implies the repair of an adequate mucosal barrier – associated with appropriate gastroduodenal and jejunal motility leading to permanent mucosal cleaning (appropriate autophagy) and microbiota diversity.

We therefore recommend introducing long term small doses maitake and/or CZM in patients with O/O or in NW patients with sarcopenia and liver steatosis or jejunal hypotonia detected by transabdominal ultrasound examination.

Please note that long term small doses of maitake also reduce the occurrence of viral infections [22].

Breath test may detect a slight increase in hydrogen or a modification in E-VOCs concentration, and ultrasound examination may detect improved motility of the foregut associated with mucosal repair.

Conclusion

Long term intake of small doses of maitake or of CZM may help to decrease body weight, especially in O/O patients. Maitake+CZM can be more beneficial in patients with NW since they may recover from jejunal hypotonia and therefore from transient vagal alteration.

The mechanisms of action are yet only hypothetical. However, improvements of the foregut motility have been objectivised. An increase in microbial diversity is possible although it probably does not play a key role. An immunostimulating effect is unlikely.

Further investigations are necessary to determine the role of autophagy and of the foregut microbiota diversity, as well as of the vagal nerve in the protection of the mucosa. However, since low amounts of maitake+/-CZM are innocuous and inexpensive, we suggest recommending such a therapy in patients with increased visceral fat, whatever the body weight.
We also suggest investigating systematically the motility of the foregut by a transabdominal examination. Exhaled hydrogen and VOCs measurement could also be usefully to detect post-therapeutic increased diversity of microbiota.

Acknowledgment(S) And Conflicts of Interest

No conflict of interest to disclose.

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