

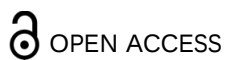


REVIEW ARTICLE

How to improve microbiota to harness chronic inflammation and prevent cancer, cardiovascular or neurodegenerative diseases? A transversal qualitative review

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ABSTRACT

Background: Dysbiosis should be controlled since it is implicated in metabolic syndrome, cancer occurrence or prognosis, inflammatory bowel diseases, periodontitis, as well as in systemic, neurological, or cardiovascular chronic inflammation.

Eradication strategies with antibiotics are in conflict with new proposals of a diversified diet to magnify the diversity of the microbiome. Probiotic use does not meet expectations.

Objective: Reconcile the different – and sometimes divergent - medical recommendations. Suggest an integrative and preventive approach that uses as little antibiotic therapy as possible, to improve the flora and to reduce silent chronic inflammation (SCI). Elaborate a simple flow chart to be used in ambulatory practice.

Methods: Identify the most frequent life-threatening diseases associated (bidirectional perspective) with altered microbiota and SCI. Specify the bacteria or viruses involved.

Select the most appropriate methods to detect, to quantify and to follow such SCI-associated dysbiosis, in usual and ambulatory practice.

Suggest inexpensive and innocuous treatments of SCI induced by dysbiosis.

Build a general model that can optimize flora quality and inflammation control, while adapting to current official recommendations.

Results: Cancer, cardiovascular and neurodegenerative diseases are the most prevalent preventable causes of death. They are frequently associated with *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, herpes viruses (herpes simplex type 1, Epstein-Barr virus or cytomegalovirus) or human papillomavirus infections. A low diversity of microbiota with low levels of hydrogen sulphide may exacerbate SCI.

SCI and dysbiosis can be detected with a breath test, detection of calprotectine and pyruvate kinase M2 in saliva. A simple flow chart may be used in ambulatory practice to control SCI.

Treatment with diet, mouth cleaning, tiny amount of essential oils and natural immunostimulating agents could improve the oral and foregut microbiota and therefore SCI.

Conclusion: Cost-effective detection and prevention of SCI could be implemented in usual practice. Its usefulness could be evaluated in a second step according to the figures available in reliable meta-analyses.

Keywords: dysbiosis – Calprotectin – breath test – PKM2

List of abbreviations:

CLP: calprotectin;
CMV: cytomegalovirus;
COVID: coronavirus 19;
EBV: Epstein-Barr virus;
FN: *Fusobacterium nucleatum*;
FODMAP: low fermentable oligosaccharides, disaccharides, monosaccharides and polyols;
H₂O₂: hydrogen peroxide;
H₂S: hydrogen sulphide;
HPV: Human Papillomavirus;
HSV1/2: herpes simplex virus types 1 or 2;
IU: international unit;
NDD: neurodegenerative diseases;
NLR: neutrophils/lymphocytes ratio;
NO: nitric oxide;
PDL1: Programmed death-ligand 1;
PG: *Porphyromonas gingivalis*;
PKM2: Pyruvate kinase M2;
SCI: Silent chronic inflammation.

Introduction

Silent chronic inflammation (SCI) is implicated in numerous local or systemic diseases.

The microbiota is defined as all the micro-organisms living on and in the human body. A pathogenic microbiota - dysbiosis - can harbour inappropriate bacteria, viruses, yeasts or parasites, leading to SCI.

Silent chronic inflammation is rarely restricted to a single organ and is rather a wide-spread issue. Therefore, in addition to its main target-organ, SCI frequently also involves the cardiovascular¹⁻³ or the central nervous system.⁴

For example, periodontitis is associated with SCI,⁵ leading to many severe diseases.⁶⁻¹² It may concern up to 70% of US adults aged 65 years and older and is associated with more than 50 systemic inflammatory disorders and comorbidities, including cancers, neurodegenerative diseases (NDD) or cardiovascular diseases.¹³ Causal relationships are not yet established. However a bidirectional effect is currently admitted.^{14,15}

Cancers are largely attributable to at least 30 modifiable risk factors including nine infectious agents accounting for 10.2% of cases, just behind smoking (15.1%), however far ahead alcohol consumption (3.2%). Strengthening efforts to reduce modifiable exposures remain central to global cancer prevention.¹⁶

Alterations in the gut microbiota frequently exist in patients with autoimmunity such as multiple sclerosis,¹⁷ lupus,¹⁸ Sjögren's disease,¹⁹ autoimmune thyroiditis,²⁰ or inflammatory bowel diseases^{21,22} and could contribute to the severity of inflammatory flare-ups.

Decreased diversity of microbiota can also be considered as a kind of dysbiosis and is frequently detected in inflammatory diseases.²³ disease,^{24,25} overweight,^{26,27} as well as neutrophilic²⁸ or eosinophilic diseases.^{29,30}

Many diseases – such as Alzheimer's disease, Parkinson's disease or depression - are associated with small intestinal bacterial overgrowth, leaky gut syndrome and vagal-mediated inflammation currently classified as gut-brain axis disorders.³¹⁻³⁴

Epstein-Barr virus (EBV) and human papillomaviruses (HPV) are known to favour many types of cancers.³⁵⁻³⁸

The association of viruses with bacteria triggers deleterious inflammation. For example, EBV may worsen *Helicobacter pylori*-induced SCI.³⁹ EBV, HPV and *Helicobacter pylori* are the most frequently reported infectious oncogenic germs.^{40,41}

There is currently no attempt to identify and list all bacteria and viruses implicated in SCI and subsequently no attempt to treat oral dysbiosis in patients with cancer, cardiovascular, central nervous system or auto-immune diseases. Silent chronic inflammation is usually controlled with systemic and symptomatic anti-inflammatory or immunosuppressive drugs which may induce severe adverse events or favour immunosuppression and consequently opportunistic infections or cancers.⁴²⁻⁴⁶

The most frequent recognized types of chronic inflammation are: visceral fat,^{47,48} chronic viral, or bacterial infections (periodontitis or dysbiosis).⁴⁹⁻⁵¹

Etiological treatments of chronic infections - such as control of dysbiosis - should be started as early as possible in order to prevent alterations of specific organs: e.g. joints, heart, arteries, skin, central nervous system, etc..

Any alleviation or control of any type of chronic inflammation should be considered as an appropriate anti-inflammatory therapy, and therefore performed in parallel with classical medical care. In addition, destruction of inappropriate germs may have important consequences on anticancer or antiviral immunity.

For example encouraging results have been reported after the improvement of microbiota due to faecal graft in patients with melanoma, renal carcinoma or non-small cell lung cancer. These improvements are attributed to the destruction of inappropriate bacteria rather than actual implantation of beneficial germs.^{52,53}

The severity of SCI is usually not quantified before immunosuppressant therapy and is not evaluated during or after immunosuppressive therapy.

More individualised clinical decision-making models should be explored. For example, white blood cell counts and exhaled-nitric oxide (NO) could be taken into account,⁵⁴ as well as neutrophils lymphocytes (NLR) ratio.⁵⁵⁻⁵⁹

Efficient, inexpensive and easy-to-use detection tools are now available to physicians who may evaluate dysbiosis and chronic inflammation.

Calprotectin (CLP) is a simple and inexpensive marker to detect oral neutrophil-induced inflammation.⁶⁰ Saliva CLP is increased in patients with periodontitis.⁶¹

Pyruvate kinase M2 (PKM2) has received increasing attention because of its role in tumour cell energy supply or proliferation, epithelial-mesenchymal transition, invasion and metastasis.⁶² Its detection in saliva has been associated with colorectal polyps, dysplasia of the stomach or of the uterine cervix, as well as multiple sclerosis or Parkinson's disease.⁶³

Hydrogen sulphite (H₂S) is a gasotransmitter which could significantly reduce chronic and degenerative diseases especially, brain, cardiovascular or kidney diseases.^{64,65}

Inducible-NO is a marker of mucosal inflammation.⁶⁶ Exhaled inducible-NO is a recognized marker of asthma, chronic cough or allergic chronic rhinitis.⁶⁷⁻⁶⁹

H₂S and inducible-NO production, estimated through the H₂S and inducible-NO levels in exhaled breath, are associated with CPL level and PKM2 detection.⁷⁰

Increasingly precise and numerous guidelines are available to manage bacterial or viral infections, or chronic inflammatory diseases. However, they do not always take into consideration the quality of the microbiota or the respect for the environment. In addition they are specific to one single disease or organ system and they do not take transversal medical issues into consideration: e.g. destruction of diversity of flora after *Helicobacter pylori*'s eradication with an increased risk of multiple sclerosis⁷¹ or Crohn's diseases.⁷²

We intended to identify and list the main bacteria and viruses undoubtedly implicated in SCI, as well as in the most frequent and severe life-threatening diseases in Europe.

The scope of the study is deliberately as broad as possible since bacteria, virus or visceral fat can involve multiple organs, impair immunity or reach functional systems such as the cardiovascular system, the autonomic nervous system or the endocrine system. As a consequence, the study may include all specific or systemic diseases which have been associated with periodontitis.¹³

The approach is integrative and transversal. The red thread of the study is to identify the germs involved in the occurrence of life-threatening diseases associated with usually undiagnosed dysbiosis-induced chronic inflammation.

We investigated what could be the place of dietetic advices, sport, antibiotic therapy or antiviral therapy

to control chronic dysbiosis and how the currently available recommendations, quality of microbiota and environment could be merged respectfully.

We will try to build an algorithm for screening and management in ambulatory medicine that takes into account all the collected elements.

In a second time and in a second article, we will try to quantify the possible benefit of such a preventive global integrative approach.

Material and methods

Only medical issues associated with frequent (prevalence >1/10.000) and potentially life-threatening diseases were included. The most recent French and European statistics, from 2022, were used.^{73,74}

Only diseases potentially induced by chronic bacterial or viral infections, or gut dysbiosis were included. We searched meta-analysis and review articles in PubMed database. Only recent articles (less than 5 years) were included. The literature search was conducted on February 2026.

Only diseases with detectable SCI during usual outpatient medical practice were included. It can be a blood or salivary test, as well as a breath test for the detection of intestinal dysbiosis.

Only preventable causes of SCI were considered. Decrease visceral fat (dietetic, physical activity, GLP1 agonists), treatment of periodontitis, treatment of dysbiosis (diet, tiny amount of essential oils, fibres), treatment of viruses such as herpes viruses (valaciclovir, immunostimulating agents), treatment of mycotoxins (decrease intake, inhibitors) will be suggested for each type of dysbiosis. We searched meta-analysis and randomized clinical trials in PubMed database. Only recent articles (less than 5 years) were included. The literature search was conducted on February 2026.

The scientific approach will be based on the following steps. See figure 1.

- Identify convincing reviews and/or meta-analyses on the most frequent life-threatening diseases which may be favoured by bacterial or viral dysbiosis.
- Identify convincing reviews and/or meta-analyses on SCI associated with such dysbiosis.
- Identify convincing reviews and/or meta-analyses on easily detectable and curable SCI in ambulatory practice. Infections which could be controlled with current innocuous and inexpensive therapy will be identified.
- Build an algorithm for screening and management of SCI in ambulatory medicine that takes into account all the collected elements. The algorithm should not lead to any lack of screening or management of at-risk condition according to available European guidelines.

Benefits which may be achieved as well as percentages of patients who may be concerned will be quantified in another work (part II).

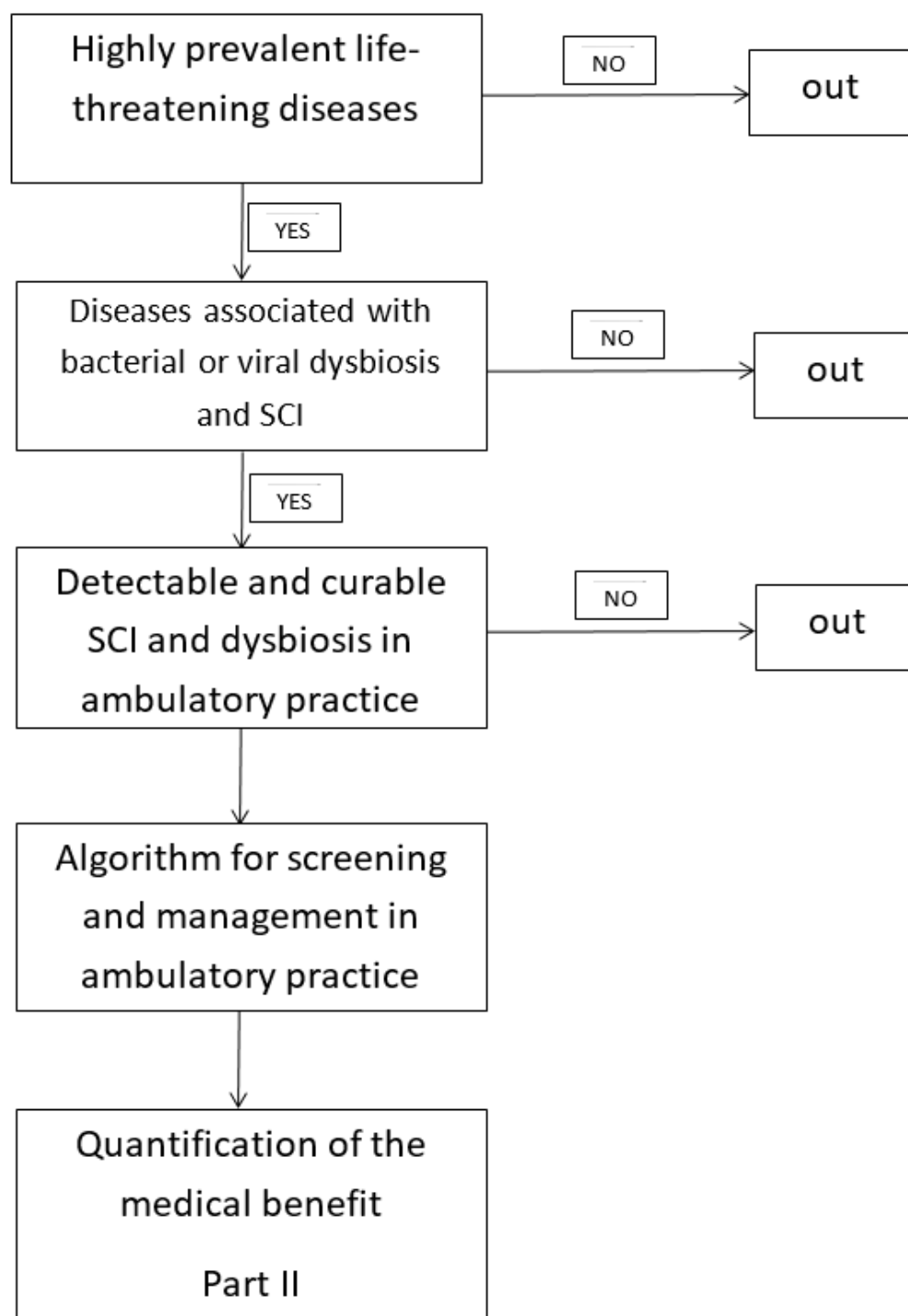


Figure 1: Steps and design of the study

Results

1. SELECTION OF THE MOST FREQUENT AND SEVERE DISEASES ASSOCIATED WITH SILENT CHRONIC INFLAMMATION AND DYSBIOSIS

The first cause of death in France and Europe is cancer, especially lung, colon-rectum or breast.^{73,74}

Lung cancer is mainly attributed to tobacco or microparticles⁷⁵ and is poorly influenced by overweight.^{76,77}

Some infectious diseases may favour its occurrence such as tuberculosis,^{78,79} or some viruses. For example cytomegalovirus (CMV), EBV and HPV are frequently associated with adenocarcinoma or non-small cell lung cancer.⁸⁰⁻⁸² Polyomavirus is also frequently found in lung cancer,⁸³ as well as hepatitis C virus.⁸⁴

A systematic review and meta-analysis demonstrated a significant association between periodontal disease and the incidence of lung cancer. Although further studies are required to eliminate confounding

factors, an implication of oral bacteria is possible.⁸⁵ *Fusobacterium nucleatum* (FN) has been particularly implicated.⁸⁶

Since FN, EBV, CMV and HPV are implicated in lung cancer, this disease is selected for this study.

Colorectal cancer - occurrence or prognosis - is associated with dysbiosis, in particular with Periodontitis and FN which is now considered as the major drivers of malignant tumorigenesis in the distal colon.⁸⁷⁻⁹¹

Fusobacterium nucleatum is probably also implicated in the occurrence of pancreatic cancer.^{92,93}

Periodontitis is associated with the occurrence of colorectal cancer.⁹⁴

In gastric cancers, a biphasic course may explain that *Helicobacter pylori* is found only at early stages of mild mucosal atrophy without dysplasia, whereas FN is found in later stages with dysplastic lesions.

Helicobacter pylori infection causes a decreased secretion of stomach acid, making it easier for oral bacteria to colonize the stomach. Solid evidences have revealed the association between oral and gastric commensal microbes other than *Helicobacter pylori* and the development of gastric cancer.^{95,96}

The incidence of gastric cancer is decreasing over time in France and in Europe.

The role of *Helicobacter pylori* is currently debated although eradication guidelines remain similar. A test for *Helicobacter pylori* infection with a positive result in adults implies an indication of treatment. The decision regarding a possible eradication treatment is therefore made before requesting diagnostic tests.⁹⁷⁻¹⁰⁰

Eradication Guidelines only concern *Helicobacter pylori* despite the probable role of viruses such as HPV, EBV or CMV.¹⁰¹⁻¹⁰⁷ Eradication is based on antibiotic therapy despite the ineluctable antibiotic resistance over time.

The eradication recommendations are restricted to patients with atrophic or lymphocytic gastritis or gastric ulcer, malt-lymphoma, or thrombocytopenia. However, *Helicobacter pylori*-eradication is widely over-prescribed.

Periodontitis is associated with gastric cancer.^{108,109}

Oral and other digestive cancers - Oesophageal carcinoma is also associated with high levels of FN.¹¹⁰

Porphyromonas gingivalis (PG) and FN, contribute to oral squamous cell carcinoma progression through mechanisms involving inflammation, epithelial-mesenchymal transition, and immune evasion.¹¹¹

Fusobacterium nucleatum is more frequently detected and in higher abundance in oral/head and neck cancer samples when compared to non-cancer samples.¹¹²

Porphyromonas gingivalis could also play an important role in oral squamous cell carcinoma development and could be involved in three different stages: epithelial-mesenchymal transition, neoplastic proliferation, and tumour invasion.¹¹³

Periodontitis is associated with an increase in oral,¹¹⁴ oesophageal,¹¹⁵ pancreatic,¹¹⁶ hepatic,¹¹⁷ and in general all digestive cancers.¹¹⁸

Most of digestive cancers are associated with oral bacteria or viruses (HPV, EBV, CMV and FN) and are therefore selected for further investigation. *Helicobacter pylori* has only been implicated in some types of gastric cancer, which is infrequent in Europe.

Breast cancers have been associated with viruses¹¹⁹⁻¹²⁶ (EBV, CMV, HPV, mouse mammary tumour virus), especially coinfection with HPV and EBV¹²⁴ or aggressive bacteria (FN, PG).¹²⁷

Lack of anti-programmed death-ligand 1 (anti-PDL1) effect, attributed to inappropriate intestinal microbiota for example post-antibiotic therapy, is well-established.¹²⁸⁻¹³⁰ Control of microbiota has been suggested to improve the efficacy of immunotherapy in oncological treatments.¹³¹⁻¹³²

Periodontitis is associated with an increased risk of breast cancer.^{133,134}

Because of the probable involvement of FN or PG, the impact of dysbiosis on the efficacy of treatment and HPV/EBV/CMV, breast cancer is selected for the study.

Prostatic cancer is associated with HPV,¹³⁵⁻¹³⁷ not with Herpes simplex virus types 1 or 2 (HSV1/2) or CMV.¹³⁸

Cancerous prostatic tissues are enriched with pro-inflammatory bacterial genera (e.g. FN, *Cutibacterium acnes*).¹³⁹⁻¹⁴¹

Prostatic cancer will therefore be included in this study.

Human papillomavirus infections: a transversal oncological issue

A specific attention should be brought to HPV infections because it may favour several types of cancers which may spuriously be split into many subgroups: oropharyngeal, gastric, pulmonary, colorectal, anal, bladder, breast or uterine cervix, etc..¹⁴²⁻¹⁴⁸ Human papillomavirus control or prevention with vaccination is therefore crucial.¹⁴⁹

Synergies between FN and HPV, HSV2, EBV have been reported.¹⁵⁰⁻¹⁵²

Periodontitis has been associated with HPV.¹⁵³

The role of HPV in ovarian cancer is controversial.^{154,155}

No convincing study is available regarding herpes virus or FN. Ovarian cancer will not be included into the study. However a link between endometriosis and ovarian cancer is likely,^{156,157} and endometriosis is potentially associated with periodontitis¹⁵⁸ and FN.¹⁵⁹

Overweight is associated with a lack of diversity in the gut microbiota.¹⁶⁰⁻¹⁶³

Surprisingly, overweight is associated with better results of check-point inhibitors efficacy.¹⁶⁴⁻¹⁶⁷ A role of chronic inflammation, of bacterial selection/ resistance and/or of viral reactivation is more likely than the paucity of diversity itself.

Accordingly, overweight has been attributed to chronic viral infections (CMV/HSV/hepatitis A¹⁶⁸ or adenovirus¹⁶⁹⁻¹⁷²).

Overweight is associated with a decreased interferon-gamma synthesis, an increased diversity of influenza viruses,¹⁷³ as well as an increased rate of viral infection.¹⁷⁴

Overweight is associated with an increased risk of breast¹⁷⁵ or colorectal cancer,¹⁷⁶ and a poorer prognosis of breast cancer patients.¹⁷⁷

Bariatric surgery dramatically reduces the risk of breast cancer.¹⁷⁸ A role of aromatase from visceral tissues is not disputed, leading to anti-aromatase therapy in oestrogen+ breast cancer.¹⁷⁹

Overweight is of course associated with cardiovascular accidents.¹⁸⁰

Overweight is therefore selected for further analysis.

Cardiovascular diseases

Ischaemic heart disease (such as heart attacks) and cerebrovascular diseases (such as strokes) account respectively for 32.4% and 20.8% of deaths from circulatory diseases.

The predominant vascular complication in Europe is coronary artery disease (31.07%).⁷⁴

Cardiovascular diseases could be partly attributed to chronic inflammation due to various metabolic conditions such as diabetes type2 or liver steatosis.^{181,182}

Other systemic chronic inflammation such as endometriosis,¹⁸³ rheumatoid arthritis,^{184,185} or psoriasis are associated with increased cardiovascular risks – mainly stroke.¹⁸⁶

Periodontitis is attributed to anaerobic bacterial and viral oral chronic infections. The enterotype of periodontitis is Prevotella and includes HP, FN and PG.¹⁸⁷

Patients with periodontitis have a significantly higher risk of stroke compared to the healthy population.¹⁸⁸⁻¹⁹²

Periodontitis is associated with carotid artery calcifications.¹⁹³

Porphyromonas gingivalis and *Aggregatibacter actinomycetemcomitans* are detected in coronary atheromatous plaque specimens of myocardial infarction patients.¹⁹⁴

Helicobacter pylori infection - especially cytotoxin-associated gene-A positive - is more frequently detected in patients with cardiovascular complications¹⁹⁵ such as coronary heart disease¹⁹⁶ or abdominal aneurysm.¹⁹⁷

Porphyromonas gingivalis antibodies are more frequently detected in patients with atrial fibrillation.¹⁹⁸

Periodontitis is associated with an increased risk of all-cause mortality: cardiovascular, cancer, coronary heart disease, cerebrovascular diseases.¹⁹⁹ Non-surgical periodontal therapy exerts beneficial effects on coronary artery disease.²⁰⁰ However, invasive dental therapy without chronic infection does not increase the risk of cerebrovascular accident.²⁰¹

Many publications report the role of acute viral infections followed with acute vascular complications: e.g. influenza, SARS-CoV-2, HIV, hepatitis C virus, and herpes zoster.²⁰²

Coronavirus19 (COVID) increases the risk of ischemic or haemorrhagic stroke,^{203,204} myocardial infarction, venous thromboembolism, ischemic stroke, major bleeding, myocarditis and global mortality, especially in men.^{205,206}

Herpes zoster is followed by an increased risk of stroke.^{207,208}

Flu may favour heart failure, arrhythmia, myocarditis 2.56%, acute myocardial infarction and stroke.²⁰⁹

After a CMV infection, the estimated increased risk of future CV disease is 13.4%.²¹⁰⁻²¹²

Epstein-Barr virus is associated with coronary artery dilation, coronary artery aneurysm, myocarditis, arrhythmias, and heart failure.²¹³

Ischaemic heart disease, cerebrovascular disease and metabolic syndrome are therefore included into the umbrella of complications driven by SCI due to chronic infections or dysbiosis. Periodontal dysbiosis (FN/PG, EBV, CMV), herpes zoster and flu appear particularly implicated in such cardiovascular complications.

Additional diseases to be considered.

Neurodegenerative diseases (NDD)

Parkinson's disease (7367 deaths per year in Europe), Alzheimer's disease (16909 deaths per year in Europe) and dementia (18138 deaths per year in Europe) may be considered as the third cause of death instead of chronic lung disease (11 486 deaths per year in Europe). The classification of an acute lung infection with chronic obstructive pulmonary disease is not relevant for an etiological approach. These *two entities* represent *different clinical* and developmental charts.

Parkinson's disease. A role of dysbiosis is well documented in the occurrence of Parkinson's disease.²¹⁴

Helicobacter pylori, hepatitis C virus and *Malassezia* have been implicated.²¹⁵⁻²¹⁷ Treatments against Hepatitis C virus reduce the risk of Parkinson's disease.²¹⁵

Influenza virus, herpes virus, hepatitis B virus, scarlet fever, mumps virus, chicken pox, pertussis, German measles, and measles were not associated with an increased risk of Parkinson's disease.^{215,218}

An implication of COVID is unclear.²¹⁹ A direct role of periodontitis is unlikely.²²⁰

Alzheimer's disease.

Infections with CMV, severe COVID, hepatitis C virus, and in general human herpesvirus are associated with an increased risk of Alzheimer's disease.²²¹⁻²²⁵

There is no statistically significant difference between the dementia group and the no dementia group regarding herpes zoster except with herpes zoster

ophthalmicus.²²⁶ The benefit of herpes zoster vaccination is therefore still debated.²²⁷⁻²²⁹

There are respectively a ten-fold and a six-fold increased risk of Alzheimer's disease when oral bacteria and PG were found in the brain.²³⁰

Periodontitis increases the risk of Alzheimer's disease.^{231,232}

Antiviral treatment or vaccination are currently discussed to prevent the occurrence of Alzheimer's disease.^{233,234}

We concluded this first part by the observation that SCI is frequently associated with all top three life-

threatening diseases and may be triggered by visceral fat, HSV1, HPV, EBV, CMV, FN or PG.

It is difficult to implicate *Helicobacter pylori* since it belongs to *Prevotella* enterotype and its eradication based on large spectrum antibiotic therapy is not specific. *Helicobacter pylori* is anyway restricted to fundus and antral carcinoma.

The causes of SCI may be entangled and bidirectional leading to vicious circles. As a consequence, eradication of a single infectious agent or any significant decrease of visceral fat may be sufficient to control chronic inflammation.

See table 1.

Table 1: Selected diseases and associated bacterial or viral dysbiosis. Identification of main pathogenic germs to be harnessed in order to control silent chronic inflammation.

Selected frequent life-threatening diseases	Associated bacterial dysbiosis	Associated viral dysbiosis
Lung cancer	Tuberculosis	HPV, EBV, CMV, hepatitis C
Colorectal, pancreatic, oesophageal cancers	<i>Fusobacterium nucleatum</i>	
Gastric cancer	<i>Helicobacter pylori</i> , <i>Fusobacterium nucleatum</i>	HPV, EBV, CMV
Oral squamous cell carcinoma	<i>Fusobacterium nucleatum</i> , <i>Porphyromonas gingivalis</i>	HPV
Breast cancer	<i>Fusobacterium nucleatum</i> , <i>Porphyromonas gingivalis</i>	HPV, EBV, CMV
Prostatic cancer	<i>Fusobacterium nucleatum</i> , <i>Cutibacterium acnes</i>	HPV, HSV1/2, CMV
Cervix uterine cancer	<i>Fusobacterium nucleatum</i>	HPV, HSV2, EBV
Overweight	Low diversity	CMV, HSV1/2, hepatitis A, adenovirus36
Cardiovascular diseases	<i>Helicobacter pylori</i> , <i>Fusobacterium nucleatum</i> , <i>Porphyromonas gingivalis</i> , <i>Aggregatibacter actinomycetemcomitans</i>	EBV, CMV, influenza, SARS-Cov-2
Parkinson	<i>Helicobacter pylori</i>	Hepatitis C
Alzheimer/dementia	<i>Porphyromonas gingivalis</i>	HSV1, Herpes zoster ophthalmicus, CMV, hepatitis C, SARS-Cov-2
Cancers, cardiovascular diseases or NDD altogether	<i>Fusobacterium nucleatum</i> , <i>Porphyromonas gingivalis</i> +/– <i>Helicobacter pylori</i> , when <i>Fusobacterium nucleatum</i> and herpes viruses are also involved	HPV, EBV, CMV, HSV1/2

2. HOW TO DETECT AND QUANTIFY SILENT CHRONIC INFLAMMATION IN AMBULATORY USUAL PRACTICE? PROPOSED ALGORITHM.

Clinical anamnesis and examination

This part will not be developed since it relies on basic clinical knowledge.

The physician will look for a medical history of cancer, severe viral infections, herpetic flares, herpes zoster, HPV positive cervical smear, cardiovascular clinical signs of allergic, inflammatory or autoimmune diseases: polyarthritis, psoriasis, endometriosis, oral or genital lichen, asthma, chronic obstructive pulmonary disease, overweight with increased waist diameter, as well as periodontitis.

Chronic viral infections

The most reliable method would be the detection of replication of virus with quantitative Polymerase Chain Reaction. It is possible in research, for EBV, CMV and HSV1,²³⁵⁻²³⁸ or HPV in routine.^{239,240}

However, it is expensive and time consuming. It cannot be performed in usual practice especially for all previously pointed infectious agents (i.e. FN/PG, oral HPV, CMV or EBV, HSV1), particularly since viruses could be detected only a few days/month despite their implication, as it has been observed in periodontitis.²⁴¹

On the contrary oral detection of HPV may spuriously generate anxiety although the virus is most likely transient and is, most of the time, not associated with an increased risk of oral cancer. For example, it appears that there is no established link between chronic HPV infection and oral cancer.²⁴²

The detection of oral HPV is therefore not recommended in usual practice.

Therefore, we suggest relying on a meticulous clinical examination and chairside tools. Quantification of inflammation and detection of dysbiosis will complete the screening.

Basic biology

For general inflammation

Absolute neutrophil count or the Systemic Immune-Inflammation Index, derived from platelet, neutrophil, and lymphocyte counts (platelets×neutrophils/lymphocytes), could be used to evaluate obesity-related inflammation. Systemic Immune-Inflammation Index may better reflect the interplay between systemic inflammation and immune suppression.²⁴³

The NLR and the systemic Immune-Inflammation Index are derived from routine blood tests – cost-effective and accessible for resource-constrained settings – and capture complementary pathophysiological dimensions: The NLR reflects neuro-inflammation *via* neutrophil-lymphocyte balance, while SII integrates platelets to reflect inflammation-thrombosis crosstalk. These parameters are predictive of the outcome of stroke.²⁴⁴

The NLR predicts the cardiovascular outcome in diabetic patients,²⁴⁵ peripheral artery diseases,²⁴⁶ depression,²⁴⁷ inflammatory bowel disease,²⁴⁸ or patients with cancer.^{55,57,249,250}

The NLR may serve as a convenient tool in monitoring psoriasis treatment and indicator of systemic inflammation.²⁵¹

The NLR may be used to evaluate the risk of hip fracture²⁵² or of sarcopenia.²⁵³

The NLR may quantify the severity of periodontitis,²⁵⁴ and is increased in patients with Alzheimer's disease.²⁵⁵

The NLR is therefore considered in this study. The cut-off value of 2.0 should be assumed as an alert threshold.^{54,248,249,256,257}

For metabolic syndrome

Waist circumference or perhaps waist to hip ratio are very good parameters to quantify and follow a metabolic syndrome.²⁵⁸ It is associated with the global risk of death.²⁵⁹

A large waist circumference is an independent factor of diabetes type 2.²⁶⁰

Glycosylated haemoglobin, glucosaemia), Insulin resistance (HOMA-IR), body mass index, triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein, along with inflammation factors such as C-reactive protein are the most classical parameters used to follow type 2 diabetic patients.²⁶¹

Homocysteine belongs to hepatic inflammatory markers, linked with obesity,²⁶ and endothelial dysfunction.²⁶³

Usual metabolic markers appear sufficient to detect SCI.²⁶¹

FibroScan® (elastometry) may be useful for staging liver fibrosis.

FibroScan® value greater than 7.0 kPa is considered to identify most adults with hepatitis B or C, or alcohol induced significant fibrosis.^{265,266}

However a precise evaluation of liver histology by computerized morphometry shows that high level of steatosis induces misevaluation of liver fibrosis by Fibroscan.²⁶⁷ As a consequence, FibroScan® cannot be used in metabolic dysfunction-associated fatty liver diseases and therefore, biological parameters are required.

Fibrosis-4 index appears particularly relevant to evaluate fatty liver diseases. A Cut-off value of 1.3 has been suggested.²⁶⁸

Detection of dysbiosis

Breath tests could be used for the detection of dysbiosis,²⁶⁹⁻²⁷¹ especially the dosage of inducible-NO and H₂S.⁷⁰

We previously suggested that H₂S and inducible-NO could be reliably detected for the screening of SCI or oral/foregut dysbiosis in patients with clinical periodontitis. The suggested cut-of values were 0.11 ppm for inducible-NO and 0.10 ppm for H₂S.⁷⁰

New markers

Salivary calprotectine

Calprotectine is mainly synthesized by neutrophils²⁷² and is a good marker of neutrophil-induced inflammation.

Faecal CLP is a recognized marker of inflammatory bowel disease with an established cut-off around 50 international units (IU)/ml.^{273,274}

Saliva CLP is increased in periodontitis,^{60,61} and in numerous severe pathologies such as cancer,⁶ metabolic syndrome,⁷ psoriasis,⁸ bone loss,⁹ dementia,¹⁰ or cardiovascular diseases,¹¹ rheumatoid arthritis,²⁷⁵ inflammatory bowel disease²⁷⁶ or oral lichen planus.²⁷⁷ Oral CLP may also be increased in infant with *Helicobacter pylori* infection.²⁷⁷

The dosage of CLP in saliva can be carried out during a simple medical consultation. Although the threshold remains to be refined, the salivary CLP could already be recognized as a reliable marker of oral inflammation. Three previous observational studies identified 750 IU/ml as a possible threshold for severe inflammation and 450 IU/ml as a possible threshold for mild inflammation.^{60,63,70}

Therefore, CPL appears to be an excellent new marker for the detection of SCI or to follow the therapeutic response.

Pyruvate kinase M2 (PKM2)

Pyruvate kinase M2 is a key enzyme for glycolysis and is closely related to tissue repair and regeneration. The switch to PKM2 modifies the glucose metabolism toward the Warburg effect which favours transformation, invasion, metastasis, and cell proliferation.⁶²

Pyruvate kinase M2 in stools is a recognized marker of dysplastic polyps of the colon-rectum.²⁷⁹

Pyruvate kinase M2 switch could also be involved in gastric cancer development.²⁸⁰

Pyruvate kinase M2 can also be measured in the saliva and is strongly correlated with oral squamous cell carcinoma progression.²⁸¹ Pyruvate kinase M2 in saliva is also associated with colorectal polyps, dysplasia of the stomach or of the uterine cervix, as well as multiple sclerosis or Parkinson's disease.^{60,63}

There is a clear association between PKM2 detection and high CLP or inducible-NO levels, or low H₂S levels.⁷⁰

The detection of PKM2 in saliva can also be carried out during a simple medical consultation. It is only qualitative. There is no published information on any quantitative approach in saliva. There is no evidence that a quantitative measure has a medical interest.

This measure might be reserved for patients with high levels of CLP in saliva.

Other tests

Oral quantitative polymerase chain reaction for oral bacteria or viruses (EBV, CMV, HSV1 or HPV) may be performed.^{282,283}

However, no consensus has been yet accepted for their use in routine detection. In addition, they are expensive and cannot help for a quick decision of further screening.

Fusobacterium nucleatum or PG may be detected by clinical examination and simple fluorescence,²⁸⁴ as well as *Cutibacterium acnes*.²⁸⁵

Endotest® is a very expensive test which cannot be used in routine ambulatory consultation. In France, Endotest® is only offered to few young women with a strong suspicion of endometriosis.²⁸⁶

Salivary proteins - such as IL1 β , IL6, IL8 or TNF- α - can be used as inflammatory markers of the oral cavity.^{287,288} However none of them can be measured by a simple inexpensive ambulatory test.

We therefore suggest relying on a thorough clinical examination with a Wood lamp and a blue light, a breath test, as well as low-cost CLP and PKM2 kits for all outpatients with a history of periodontitis.

Proposed algorithm for the detection of silent chronic inflammation

We previously suggested a practical ambulatory approach in all patients with oral or digestive symptoms in order to detect SCI.⁷⁰ See figure 2.

First step: Breath test and oral examination should be performed in all patients with abdominal complaints.

Second step: Salivary CLP dosage should be performed in all patients with periodontitis and abnormal breath test results.

Third step: The detection of PKM2 will be reserved for patients with CLP levels ≥ 750 IU/l.

This screening is innocuous and inexpensive. It may enable early detection of severe ongoing inflammatory stage and stop there evolution toward cancers, cardiovascular/metabolic or neurodegenerative diseases.

It may also have beneficial effects on other severe dysbiosis-associated diseases. For example, FN and PG control may reduce the risk of inflammatory bowel disease, especially of haemorrhagic colitis,²⁸⁹ of endometriosis,²⁹⁰ of periodontitis and all associated diseases.^{291,292}

The control of viruses may also decrease the risk of transformation of asymptomatic monoclonal gammopathies in myeloma or lymphoma.²⁹³

Joint pain²⁹⁴ or depression^{295,296} may also be alleviated by the improvement of gut microbiota.

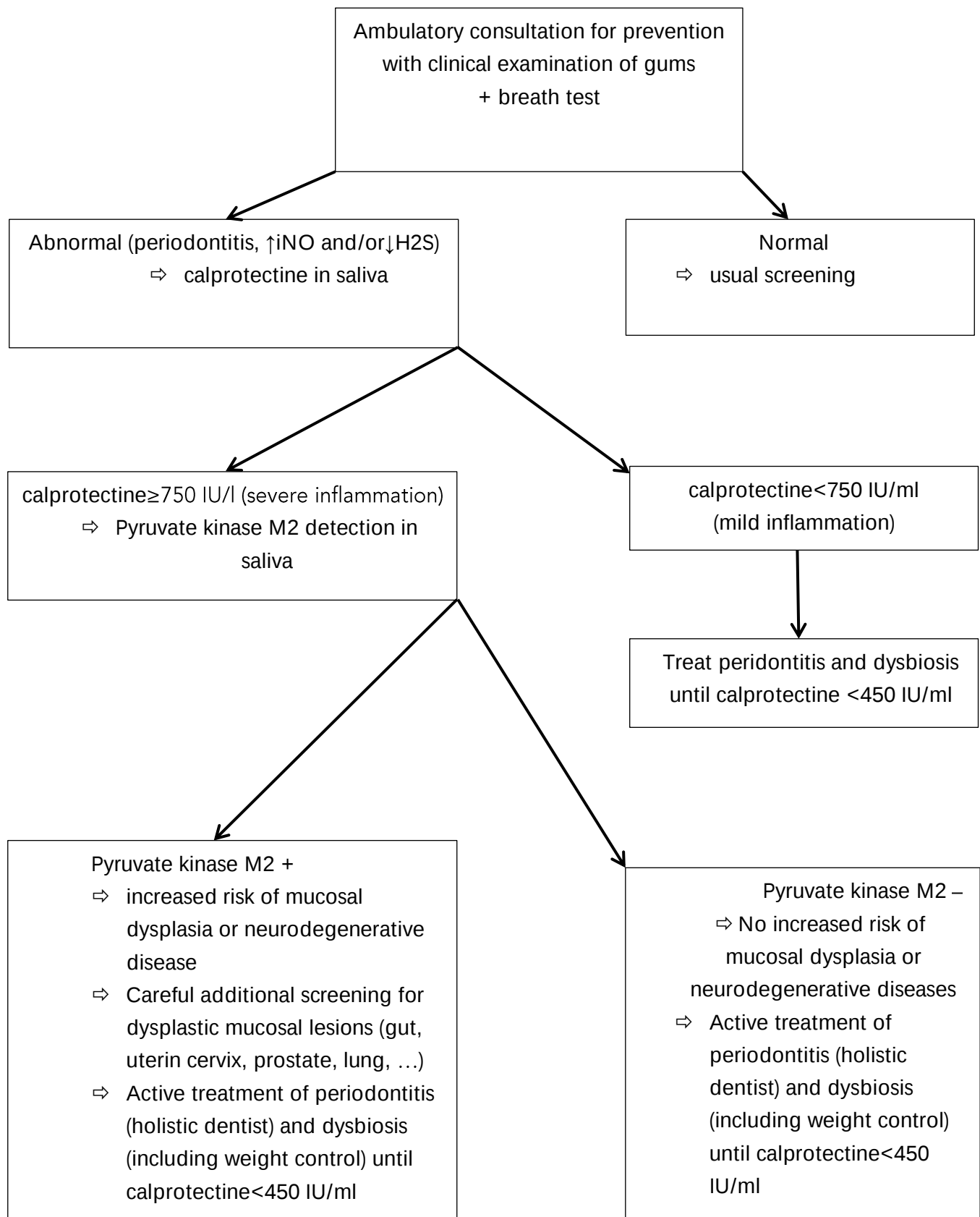


Figure 2: Proposed algorithm for the early detection of mucosal or brain chronic inflammation based on breath test, and calprotectine or pyruvate kinase M2 detection in saliva.

3. IDENTIFICATION OF INNOCUOUS AND INEXPENSIVE THERAPY TO CONTROL SILENT CHRONIC INFLAMMATION. PROPOSED GLOBAL INTEGRATED TREATMENT.

Treatments to be selected should have a very favourable risk/benefit ratio for the patients, for the environment and low cost because they should be used on a long term period, for a large part of the population, without severe life-threatening diseases yet. The treatments should not induce germ-resistance or any destruction of the microbiota which may end to low diversity, decreased immunity or overweight.

Goals are entangled: clear periodontitis, reduce visceral fat and improve diversity of microbiota with an increase of NO (without inducible-NO increase) and H₂S, as well as PDL1 inhibition. This will decrease chronic inflammation, immunosuppression and chronic systemic damages. The stimulation of immunity will help to control herpes viruses or HPV.

Treatments should act synergically, based on firstly harmless tiny doses, secondly the same narrow target tackled simultaneously, thirdly adapted to a large diversity of situation which represents the diversity of enterotypes, immunotypes and systemic inflammation/organ defects encountered in real life medicine.

For all these prerequisites, we try to select natural products, considered as food, spices or aromatic natural products rather than medications or foods complements which may firstly induce adverse events, secondly contain excipients or contaminants and thirdly contain no or low amount of fibres and are devoid of natural beneficial endobiota.

Such products should be consumed in tiny amounts on a long term basis.

They should fit into a global lifestyle change with diet, brain training, decreased stress and increased physical activity.

Probiotics have failed to control cancer, overweight, cardiovascular diseases, NDD, viral infections. In

addition they cannot be considered as natural products.

Clear periodontitis = Control *Fusobacterium nucleatum*, *Porphyromonas gingivalis* and herpes viruses

Fusobacterium nucleatum and PG are anaerobic bacteria implicated in periodontitis.²⁹⁷

Periodontitis can be controlled by non-surgical treatment with mechanical mouth cleaning,⁵³ photobiomodulation,²⁹⁸ or mouth wash with 1% hydrogen peroxide (H₂O₂).²⁹⁹⁻³⁰²

Hydrogen peroxide is also efficacious against SARS-COV-2 and herpes simplex.³⁰³⁻³⁰⁴

Vitamin D supplementation may promote autophagy of PG.³⁰⁵

We selected personal mechanical mouth cleaning, hydrogen peroxide mouth wash and vitamin D supplementation.

Reduce visceral fat with diet or lipase inhibition

Low carb and low caloric diets are necessary to control visceral fat. Diet or the use of medications such as GLP1 agonist will not be discussed here. Intermittent fasting³⁰⁶ with low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) intake^{307,308} could be suggested.

Overweight and visceral fat is associated with decreased microbial diversity. Increased diversity cannot be achieved by destruction of the remaining flora but with diversification of fibres and therefore vegetables.³⁰⁹

An increased intake of organic vegetables is a well-established recommended diet for body weight, CV diseases or cancer.³¹⁰⁻³¹⁴

The intake of fibres is also beneficial in Crohn's disease.³¹⁵

Tiny amount of essential oils may decrease the amount of undesirable bacteria and increase diversity.^{316,317}

For example, *Cinnamomum verum* or *Origanum vulgare* could be efficacious against FN and periodontitis at very low dose.^{318,319}

Oral microbiota produces nitrite leading to the synthesis nitric oxide.^{320,321}

Nitric oxide possesses antiviral (SARS-CoV-2, herpes, HPV).³²²⁻³²⁹

Altered endogenic NO production may favour breast³³⁰ or prostatic cancer occurrence.³³¹

An improvement of diversity will improve the efficacy of PDL1 inhibition.^{131,132}

Laetiporus sulphureus or *Grifola frondosa* are documented inhibitors of lipase.^{332,333}

We suggest a low-caloric diet, and low intake of FODMAPs in association with tiny amounts of essential oils such as *Origanum vulgare*, *Cinnamomum verum* or *Citrus lemon*, *zinziber officinale* in association with either *Grifola frondosa* (maitake) or *Laetiporus sulphureus*.

Stimulation of immunity will help to control herpes viruses or human papillomavirus.

Coriolus versicolor is a well-documented immunostimulating mushroom. It may increase the survival of patients with adenocarcinoma, especially of the stomach or of the colon.^{334,335}

It has anti-viral properties against HPV, EBV, herpes simplex,³³⁶⁻³³⁹ or even SARS-CoV-2.³⁴⁰

The association valaciclovir + *Coriolus versicolor* is associated with a decreased risk of myeloma or lymphoma in asymptomatic monoclonal gammopathy.²⁹³ However the long term use of valaciclovir does not belong to usual recommendations.

Coriolus versicolor has also been reported to decrease Alzheimer's disease in a mouse model,^{341,342} and clear prion or intracellular bacteria.³⁴³⁻³⁴⁹

It modulates Toll-Like Receptor,^{346,347} and inhibits many mycotoxins.³⁴⁸

Phellinus linteus is also a strong immunostimulating agent with anticancer properties.³⁴⁹ It is efficacious against periodontitis.^{350,351}

Ganoderma lucidum could, when added to quercetin, control EBV in mice.³⁵²

Proposed global integrative treatment with low risk and low cost

According to the results, we suggest a very limited number of actions to control SCI.

Firstly, mechanical mouth cleaning with hydrogen peroxide mouth wash, *Coriolus versicolor* +/- *Ganoderma lucidum* or *Phellinus linteus*, vitamin D and tiny amounts of essential oils, especially *Origanum compactum*.

Secondly, decrease visceral fat with specific diet, *Grifola frondosa*, *Laetiporus sulphureus* and tiny amount of essential oils, especially *Origanum compactum*, *Cinnamomum verum*, *Citrus lemon* or *Zinziber officinale*.

Thirdly, increase organic food (especially green vegetables and fibres), which probably contains endobiota and natural polyphenols. Please note that food complements do not contain endobiota and cannot increase microbiota diversity.

Periodontitis, body weight, waist diameter, NLR, breath test, CLP and when needed PKM2 appear valuable parameters for annual or biannual surveillance.

Discussion

The most frequent causes of death are undisputedly cancers, cardiovascular diseases and neurodegenerative diseases.

The currently used classifications may lead to spurious conclusion regarding aetiology. Some diseases are classified according to organs (heart disease), others according to the pathology (cancer), others according to clinical signs (neurodegenerative diseases).

In order to prevent disease, it is necessary to tackle the causes. Therefore, an etiological approach is suggested.

We focussed on the causes of chronic inflammation, e.g. frequent viral or bacterial infections and/or visceral fat.

Tobacco or alcohol abuse, although largely implicated in cancer and cardiovascular diseases does not belong to dysbiosis related causes.

The most frequent causes of death are at least partly explained by chronic infections and/or dysbiosis

Surprisingly a very limited number of infectious agents are implicated: few oral bacteria, herpes viruses or HPV, dysbiosis-related visceral fat.

According to the "Consortium milieu intérieur", the quality of immunity could be evaluated from only three main factors, tobacco, CMV serology and BMI.³⁵³

However, oral inflammation appears to be a cornerstone of SCI and foregut dysbiosis.

Periodontitis is associated with silent chronic inflammation and many severe diseases.⁶⁻¹² It may concern up to 70% of US adults aged 65 years and older and is associated with more than 50 systemic inflammatory disorders and comorbidities.¹³

Considering that periodontitis treatment or prevention could decrease the frequency and the severity of many systemic infections or chronic diseases, oral evaluation of SCI appears mandatory in all patients. It could start with clinical examination of gums, maybe with the help of a Wood lamp and a blue light.^{284,285}

Oral bacteria build biofilms and conjugate their competence to destroy proteins and to generate permeability, inflammation and immunosuppression leading to excessive repair involving epithelial-mesenchymal transition.³⁵⁴

Viral infections - especially EBV or HPV are able to induce mutations and therefore to increase the risk of tumor.³⁵⁵

Global Mechanism of destruction and inflammation. The need of synergic enzymes of deleterious infectious agents

Fusobacterium nucleatum does not possess protease and cannot induce chronic inflammation alone.

The destructive process requires proteases from PG³⁵⁶ or *Aggregatibacter actinomycetemcomitans*³⁵⁷ in the mouth or from *Gardnerella vaginalis* on the cervix to alter the mucosa. This cutting of mucus enables a cross-feeding which supports mutualism.¹⁵⁰

When protease are inhibited, the pathogenic process is disrupted.³⁵⁸

Aggregatibacter actinomycetemcomitans protects PG³⁵⁹ from H₂O₂ produced by commensal beneficial bacteria.³⁶⁰

Phellinus species are mushrooms which contain strong protease inhibitors,^{361,362} and therefore may protect the gingiva.^{350,351}

*Coriolus versicolor*³⁶³ inhibits Toll-Like-Receptor4 which is a key receptor implicated in oral inflammation induced by anaerobic bacteria.^{364,365}

Fusobacterium nucleatum may co-aggregate with *Candida albicans*, *Cutibacterium acnes*, or *Streptococcus cristatus* leading to mutual attenuation of virulence, which promotes a long-term persistence within the oral cavity, especially in endodontic lesions. Long lasting lesions are therefore able to survive to short term treatments.³⁶⁶⁻³⁶⁸

Fusobacterium nucleatum favours the occurrence of HPV-induced intraepithelial neoplasia on the cervix.³⁶⁹⁻³⁷¹

Fusobacterium nucleatum is able to target sugars of numerous tumours (stomach, prostate, ovary, colon, uterus, pancreas, breast, lung, and oesophagus)³⁷² and favour tumour spread.³⁷³

Fusobacterium nucleatum in excess is frequently found in patients with severe haemorrhagic colitis.³⁷⁴ This latter disease dramatically increase the risk of digestive tumours (odd ratio between 3.0 to 6.0).³⁷⁵

Concomitant CMV infection may lead to methylation of the gene of interferon-gamma³⁷⁶ and herpes simplex flares may favour the appearance of anti-interferon-gamma antibodies.³⁷⁷ Both mechanisms end to immunosuppression.

Protection by gasotransmitters (hydrogen sulphide and nitric oxide) and diversified gut microbiota

The diversity of microbiota of the foregut could be estimated with the exhaled-H₂S level. Hydrogen sulphide is a gasotransmitter with supposed anti-aging properties and which could significantly reduce progressive, chronic, and degenerative diseases especially, brain, cardiovascular or kidney disease.⁶⁴

Accumulative data suggest that H₂S may have biphasic effects. At low levels it has anti-inflammatory and antioxidant roles. However, it has pro-inflammatory effects under certain conditions where rapid release of H₂S in tissues occurs, such as sepsis.³⁷⁸

In healthy conditions, H₂S-related enzymes are expressed in human lungs, where they have mucolytic, antioxidant, anti-inflammatory, and antibacterial roles, thus contributing to airway epithelium homeostasis.³⁷⁹

In published studies, the mean H₂S levels range from 0.01 ppm in chronic pulmonary disease or type 2 diabetes mellitus^{380,381} to 0.08 ppm in patients with digestive diseases including colorectal cancers.³⁸² We previously published results within the same range in patients with colonic polyps.³⁸³

Hydrogen sulphide works with NO to induce vasodilation and angiogenesis in a cooperative manner.^{65,384}

Nitric oxide production depends mainly on oral flora and of the transformation of nitrate to nitrite.^{320,321}

In lung, NO reacts with oxyhaemoglobin with high affinity and is rapidly scavenged in red blood.³⁸⁵ Therefore, the low levels of NO produced locally are not exhaled.

However, a biphasic effect has been described. High levels of NO can be produced by immune

cells and is called inducible-nitric oxide (inducible-NO). Inducible-NO reacts with superoxide, resulting in peroxynitrite formation and cellular toxicity.³⁸⁶ It is a marker of mucosal inflammation.⁶¹

In recent reviews of literature, exhaled inducible-NO ranges from 0.02 ppm to more than 0.05 ppm when chronic inflammation is expected.^{48,387} It is increased in many inflammatory diseases such as systemic lupus erythematosus,³⁸⁸ asthma,³⁸⁹ psoriasis,³⁹⁰ heart failure³⁹¹ or inflammatory bowel diseases.³⁹² The cut-off could be 0.11 ppm for iNO.⁶⁰

Dysbiosis of the foregut may be split into two groups: decreased diversity or overgrowth of undesirable bacteria named small intestinal bacterial overgrowth.

Small intestinal bacterial overgrowth usually develops in the ileum, not in the foregut. It can be diagnosed with the detection of hydrogen in exhaled air.²⁶⁹ The measurement is performed after a fasting period longer than 10 hours. After fasting, hydrogen level should be very low except in case of ongoing mucosal destruction (e.g. celiac disease or ongoing viral infection). Hydrogen is not increased in case of silent chronic inflammation.²⁷⁰

Accordingly, ambulatory consultations should mainly focus on oral bacteria linked to periodontitis and to decreased global diversity.

Markers of decreased diversity

Decreased diversity is associated with overweight³⁹³ or inflammatory bowel diseases.³⁹⁴ Cancer may also be associated with decreased amount of small chain fatty acids – attributed to low diversity in the colon.³⁹⁵ A decrease in diversity - for example after antibiotic therapy – has also been implicated in the attenuation of checkpoint inhibitor efficacy.³⁹⁶

Less community richness was also observed in the poststroke patients, with consequences on the prognosis.³⁹⁷

Small chain fatty acids levels can be low and associated with decreased diversity.³⁹⁸ They can be high and associated with gut dysbiosis, gut permeability,

excess adiposity, and cardio-metabolic risk factors³⁹⁹ or with periodontitis.⁴⁰⁰ However, contradictory results have been reported with periodontitis.⁴⁰¹ Small chain fatty acids measures are therefore difficult to interpret.

Furthermore, measurement of small chain fatty acids requires complicated and expensive devices such as Xpid-9500® which cannot be easily implemented in usual practice.⁴⁰² Dosage of small chain fatty acids will not be considered

Decreased endogenous NO impairs gastric emptying⁴⁰³ which is almost always found in patients with overweight.⁴⁰⁴

Glucagon-Like-Peptide1 agonists are known to worsen gastric emptying which may reduce food intake.⁴⁰⁵

Overweight is associated with altered microbiota and low diversity.^{165,167,406}

The efficacy of GLP1 agonists is correlated with increased diversity of the microbiome.⁴⁰⁷

It would appear that *Akkermansia muciniphila*, and other bacteria producing short-chain fatty acids enhance GLP-1 agonists' efficacy by improving insulin sensitivity and stimulating endogenous GLP-1 secretion. Conversely, dysbiosis characterized by reduced microbial diversity and increased lipopolysaccharide-producing pro-inflammatory bacteria correlates with poor therapeutic response. Furthermore, GLP-1 agonists may exert beneficial modulatory effects on the gut microbiota itself, indicating a bidirectional relationship.⁴⁰⁷

We hypothesize that the increase in the diversity of microbiota is a key factor influencing body weight loss. We therefore consider that oral cleaning in order to increase oral diversity and decrease *Prevotella* dominance is required for weight control.

The most important targets are FN and PG. They are anaerobic and sensitive to H₂O₂.

Fusobacterium nucleatum and PG are sensitive to tiny amounts of essential oils.^{319,408-412}

Suggested integrative innocuous therapeutic approach to control oral and digestive viruses

All targeted viruses (HPV, HSV1, CMV or EBV) are at least partly sensitive to *Coriolus*, *Phellinus* or *Ganoderma*.

Coriolus versicolor possesses well documented immunostimulating^{314,315} and anti-viral properties.³¹⁶⁻³⁴⁰ Its efficacy against HPV is demonstrated.

It may be associated with *Ganoderma lucidum* against HSV1, HPV or EBV.³³⁷⁻³³⁹

Ganoderma lucidum could, when added to quercetin further control EBV.³⁵²

Phellinus is also be added since it is efficacious against periodontitis,^{350,351} may inhibit catalase (which destroys H₂O₂) produced by *Aggregatibacter actinomycetemcomitans*.⁴¹³ *Phellinus* may also protect against flu (H5N1).^{363,414,415}

Previous observational studies suggest that the efficacy of these natural therapy are close to 80% for EBV,³³⁸ 88% for HPV,³³⁷ 95% for HSV,³³⁶ and 95% for inflammatory bowel disease.³¹⁷

Additional plants which are considered as food products could be added to control HSV1: such as *Geum urbanum*,⁴¹⁶ *Prunella vulgaris*,⁴¹⁷ or *Rumex acetosa*.^{418,419}

Please remember that diversification of diet with organic green vegetables which contains fibres and endobiota are expected to increase the diversity of microbiota, whereas H₂O₂ will kill undesirable bacteria.

Cruciferous vegetable intake appears to decrease the risk of breast cancer.⁴²⁰

Please note that shiitake is excluded since it may induce severe allergic reaction⁴²¹⁻⁴²⁸ and is overpassed by *Coriolus*, *Ganoderma* and *Phellinus* species.

We therefore consider that natural antibacterial oral agents and natural antiviral agents may enable to control all the agents and pathological biofilms

which are associated with the three major causes of death in Europe: cancers, cardiovascular diseases and neurodegenerative disease.

The quantity of these natural food products to be ingested per day and the duration of diet remain to be defined. However 400 mg appears to be enough according to yet available observational studies involving several thousands of patients.

The duration should last several months or even years per principal to modify immunity, microbiota, visceral fat and the autonomic nervous system.

How to detect silent chronic inflammation and to quantify improvement

Neutrophils/lymphocytes ratio is probably the most cost-effective and accessible blood test.²⁴³

Only basic blood tests and fibrosis-4 index are required for detection and quantification of metabolic syndrome.^{263,268}

Paucity of diversity and inflammation will be assessed by a breath test with the measurement of H₂S and inducible-NO.

A previous observational study confirms that higher inducible-NO levels are associated with high CLP levels while a higher H₂S levels - assumed to be associated with diverse flora – is a marker of mild or lack of inflammation and that the Xam-8000® device can be used to detect H₂S and iNO for the screening of silent chronic inflammation or oral/foregut dysbiosis in patients with clinical periodontitis.⁷⁰

This first step (clinical examination + breath test) allows deciding when a CLP dosage in the saliva should be carried out.

These markers will complete the clinical examination in ambulatory medicine.

Salivary calprotectin and oral evaluation of neutrophilic chronic inflammation

Periodontitis is associated with an increased level of CLP in saliva.^{60,61}

Serum CPT is an excellent marker of COVID severity, prognosis or recovery.⁴³⁰⁻⁴³⁹

Although the thresholds remain to be refined, the salivary CLP level could be acknowledged as a reliable marker. We previously suggested the threshold of 750 IU/ml.⁷⁰

Pyruvate kinase M2 detection in saliva: the risk of cancer or of neuro-inflammation

Pyruvate kinase is a key enzyme for glycolysis and is closely related to tissue repair and regeneration. The switch to PKM2 modifies the glucose metabolism toward the Warburg effect which favours transformation, invasion, metastasis, and cell proliferation.⁶³

Pyruvate kinase M2 can be measured in the saliva and is strongly associated with oral squamous cell carcinoma progression,²⁸⁰ with colorectal polyps, dysplasia of the stomach or of the uterine cervix, as well as multiple sclerosis or Parkinson's disease.^{60,63}

Pyruvate kinase M2 in stools is a recognized marker of dysplastic polyps of the colon-rectum.²⁷⁸

Pyruvate kinase M2 switch could be involved in gastric cancer development.²⁷⁹ *Helicobacter pylori* is a recognized cause of non-cardia gastric cancer.⁴⁴⁰

We suggest that the detection of PKM2 could be reserved for patients with high levels of CLP in saliva, as well as low H₂S and high iNO levels in breath. All three items are markers of mucosal chronic inflammation associated with predictable atrophy/dysplasia.

Practical suggested global and integrative ambulatory approach

We propose the following algorithm to detect SCI in ambulatory usual practice. See figure 2.

First step: Breath test and oral examination should be performed in all patients with abdominal complaints or clinical periodontitis.

Second step: Salivary CLP dosage should be performed in any patients with abnormal breath test

results or in any patients with systemic inflammatory disease or risks factor for cancer or NDD.

Third step: The detection of PKM2 will be reserved for patients with increased CLP levels, and abnormal breath test results or clinical periodontitis.

This screening is innocuous and inexpensive. It may enable early detection of severe ongoing inflammatory stage and stop there evolution toward cancer of Parkinson or Alzheimer or osteoporosis.^{60,63}

Clinical implications and future directions

This work confirms the hypothesis that high salivary CLP is associated with foregut dysbiosis and PKM2 switch with possible severe consequences such as dysplastic lesions of gut or uterine cervix or NDD.

After breath test, we suggest that salivary CLP could be an adequate pre-screening marker for oral or digestive cancers in patients with periodontitis and *Fusobacterium nucleatum*/*Porphyromonas gingivalis*.

The flow chart depicted in figure 2 is not time consuming, and appears reliable to detect silent chronic inflammation which may spread down-ward or to the brain.

This part could be completed with the quantification of the medical benefit related to the control of SCI induced by oral bacteria or viruses which could be controlled by currently available inexpensive and innocuous medications or dietary supplements.

Conclusion

Silent chronic inflammation is not due to a single cause, entanglement is almost constant.

Several organs are concerned: nervous central system + cardiovascular system + specific organ.

A simple flow chart for early detection of dangerous chronic inflammation of the mouth or of the foregut can be applied in ambulatory medicine.

We suggest its application in all patients with oral or digestive symptoms.

This early detection is essential because treatments to reduce oral inflammation or methods to detect complications are available.

Neglecting this simplistic approach could signify heavy loss of chance for a large proportion of the population.

However, further studies are required to refine the threshold levels for CPL or H2S/NO levels for example according to the age, underlying vascular conditions or perhaps gastric emptying and gastroesophageal reflux.

Long-term observational studies could assess the value of reducing salivary CLP through local care and see the preventive effect of the control of inflammation on gut dysbiosis, body weight, dysplastic mucosal lesions, some cancers, osteoporosis, alveolar bone loss, anxiety-depression episodes, etc.

Conflict of interest:

DFN sarl. Farming business. Production of organic natural flavors

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