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High Salivary Calprotectin is Associated with Low Exhaled Levels of Hydrogen Sulphide (H2S) and High Exhaled Inducible-Nitric Oxide (iNO)

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Abstract

Background: Salivary calprotectin (CPL) is a marker of neutrophil-induced inflammation, associated with periodontitis (PO). Inducible-nitric oxide (iNO) is a marker of eosinophilic inflammation. Hydrogen sulphide (H2S) is a marker of antioxidative activity, vasodilatation and good diversity of gut microbiota.

Objective: Assess whether high salivary CPL, measured in patients with PO, is associated with high or low levels of exhaled iNO or H2S. Suggest an algorithm for detection of silent chronic inflammation.

Methods: All relevant data were collected from patients who consulted from 2025 January 2nd to June 30th and who had a medical history of periodontitis (PO). Patients were classified according to the level of salivary CPL (group1 ≥750 ui/ml and group2 <750 ui/ml).

Results: 187 patients were included: 54 in group1 and 133 in group2. Higher levels of iNO were associated with high levels of salivary CLP (0.125+/-0.029; [0.117; 0.133] versus 0.106+/-0.048; [0.098; 0.114]; p<0.001). Detection of pyruvate kinase M2 (PKM2) was more frequent in patients with high CPL (46.3% versus 11.7%; p<0.001). H2S levels were higher in patients with low CPL (0.108+/-0.040; [0.101; 0.116] versus 0.092+/-0.045; [0.079; 0.104]; p<0.01; trend)), especially in patients with low iNO levels (trend).

Conclusion: Oral inflammation is associated with higher detection of PKM2, lower levels of H2S and higher levels of CPL or iNO. We hypothesize that silent chronic inflammation could be routinely detected with a breath test and in case of abnormal results be quantified with CPL or PKM2 measurement in saliva. A screening algorithm is suggested. The validation of thresholds and algorithm should be validated by further studies.

Keywords: Calprotectin; Nitric Oxide, Hydrogen Sulphide; PKM2

List of Abbreviations: CLP: calprotectin; CMV: cytomegalovirus; HP: Helicobacter pylori; HPV: Human Papillomavirus; iNO: inducible-nitric oxide; NDD: neurodegenerative diseases; PKM2: Pyruvate kinase M2; PO: periodontitis; SCFA: small chain fatty acids; SD: standard deviation; SIBO: small intestinal bacteria overgrowth.

Introduction

Calprotectin (CLP) is a simple and inexpensive marker to detect oral neutrophil-induced inflammation [1, 2]. Saliva CLP is increased in patients with periodontitis (PO) [3] which is associated with severe pathologies such as cancer [4], metabolic syndrome [5], psoriasis [6] as well as bone loss [7], or brain [8], cardiovascular [9], or joints inflammation [10], all of which requires active prevention.

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 [11]. 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 [12].

Hydrogen sulphite (H2S) is a gasotransmitter which could significantly reduce chronic and degenerative diseases especially, brain, cardiovascular or kidney diseases [13].

H2S works with nitric oxide (NO) to induce vasodilation and angiogenesis in a cooperative manner [14, 15].

NO production depends mainly on oral flora and of the transformation of nitrate to nitrite [16, 17].

In lung, NO reacts with oxyhaemoglobin with high affinity and is rapidly scavenged in red blood [18]. 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 (iNO). Inducible-NO reacts with superoxide, resulting in peroxynitrite formation and cellular toxicity [19]. It is a marker of mucosal inflammation [20].

Exhaled iNO is therefore a recognized marker of asthma, chronic cough or allergic chronic rhinitis [21-23], systemic lupus erythematosus [24] or progressive cancer [25].

We investigated whether the iNO and H2S production, estimated through the iNO and H2S levels in exhaled breath, are associated with CPL level and PKM2 detection.

We took the opportunity of this observational study to investigate whether Helicobacter pylori (HP) or cytomegalovirus (CMV) infection could be confounding factors.

Material and Methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations, from 2025 January 2nd to 2025 June 30th.There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before data collection. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, accord-

ing to the International Committee of Medical Journal Editors (ICMJE). French legislation does not require the consent of an Institutional Review Board in such epidemiological studies.

Inclusion Criteria: All patients with a medical history of PO were included. Patients signed a written consent for the possible retrospective use of the anonymized collected data.

Exclusion Criteria: Lack of signed consent for possible retrospective epidemiological use of data; incomplete information on age, weight, height, breath tests, CMV-serology, HP-serology, oral CLP or PKM2 level, medications. All this information should be available.

Patients treated with strong anti-inflammatory treatment known to decrease TNF levels (such as methotrexate, steroids, anti-TNF antibodies) were excluded because they can induce a bias on the measurement of salivary CLP.

Gas Measurement: The patient comes after at least 10 hours of fasting. He /she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air of the lungs in a first neutral plastic bag (1.3 litre). The air is analysed by the device Dräger X-am® 8000 [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure H2S or iNO.

This device is easily portable and equipped with a powerful pump.

The device's calibration is regularly performed by Gazdetect France® with H2, H2S and NO. Detection limits are 1 to 250 ppm for H2, 0.02 to 20 ppm for H2S or NO.

Dosage of Salivary CLP: Bülhmann laboratories AG (Schönenbuch, Suisse) currently commercializes an ambulatory kit for the quantitative dosage of faecal CLP.We used this device for the dosage of salivary CLP according to the same protocol. We used 0.5 ml of saliva instead of 0.5 g of stools.

Detection of PKM2: Schebo biotech AG (Giessen, Germany) currently commercializes an ambulatory kit for a qualitative PKM2 test in faeces.

We used this device for the dosage of salivary PKM2 according to the same protocol. We used 0.5 ml of saliva instead of 0.5 g of stools.

Statistics

Comparisons of percentages or means used two-sample t-tests.

Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p<0.001$.

95% confidence intervals were calculated when p values were <0.01.

Limitations of the Study

All inflammatory diseases were documented. No patient was treated with corticosteroids, NSAIDS or immunosuppressant therapy. Three patients with rheumatoid arthritis treated with methotrexate or anti-TNF antibodies) were discarded for this reason. No treatment was therefore expected to have a significant impact on oral inflammation. However, other confounding factors are possible.

The very limited number of exclusions enables to conclude that no recruitment or selection bias is expected. However, all patients were Caucasian. Our conclusions may therefore be limited to a Caucasian population.

Results

This descriptive observational epidemiological study includes 187 patients.

Comparison of Groups 1 And 2, According To CPL Levels (See Table 1 And Table 2)

The two groups were similar for age, weight, height, gender, HP-serology or CMV-serology. However they were different regarding the detection of PKM2 in saliva. PKM2 detection was more frequent in patients with elevated CLP ($p<0.001$ between group 1 and group 2). Interestingly, iNO levels were higher in group 1 ($p<0.001$) and H2S levels were higher in group 2 ($p<0.01$, trend). PKM2 detection was particularly infrequent when CLP was lower than 750 ui/ml.

We concluded that CPL dosage is firstly associated with increased iNO and PKM2 detection and secondly inversely associated with a good diversity of oral flora (high H2S levels).

Table 1: Demographic Data for Group1 and Group2

	Gender	Age	Weight	Height
	(% of female)	(years)	(kg)	(cm)
Group 1 (CPL≥750)	80	59+/-12	64+/-13	167+/-8
54 patients				
Group 2 (CPL<750)	71	55+/-13	63+/-15	167+/-10
133 patients				
P values	>0.05	>0.05	>0.05	>0.05

Table 2: HP or CMV Serologies, PKM2 Detection, and Exhaled H2S or Ino Levels per Group

	CMV (IgG)	HP (IgG)	PKM2 +	H2S in ppm	iNO in ppm
	(% positive)	(% positive)	(% positive)	Mean+/-SD	Mean+/-SD
				[Confidence interval]95%	[Confidence interval]95%
Group 1 (CPL≥750)	52	14.3	46.3	0.092 +/-0.045	0.125 +/-0.029
54 patients				[0.079; 0.104]	[0.117; 0.133]
Group 2 (CPL<750)	42.9	14	11.7	0.108 +/-0.040	0.106 +/-0.048
133 patients				[0.101; 0.116]	[0.098; 0.114]
P values	>0.05	>0.05	**<0.001**	**<0.01**	**<0.001**
				(trend)	

Discussion

Periodontitis: A Key Symptom to Prompt Further Investigations

PO is associated with silent chronic inflammation and many severe diseases [4-10]. 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 [26]. Causal relationships are not yet established. However a bidirectional effect is currently admitted [27, 28].

Considering that PO treatment or prevention could decrease the frequency and the severity of many systemic infections or chronic diseases, oral evaluation of silent chronic inflammation appears mandatory in all patients. It could starts with clinical examination of gums, maybe with the help of blue light [29].

Omics tools are available to investigate oral bacteria or herpes viruses. However, no consensus has been yet accepted for their use in routine detection [30]. In addition, they are expensive and cannot help for a quick decision of further screening.

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

Oral or Foregut (Mouth to Jejunum) Dysbiosis: Why Should We Measure Global Diversity, Drop Faecal Analysis, Drop SCFA Quantification and Rely On Exhaled H2S And Ino

Oral bacteria translocate to the gut through an enteral route, influencing gut microbiota and metabolism. Oral pathobionts associated with PO are implicated in gut pathology, including inflammatory bowel disease and colorectal cancer. Conversely, mechanisms by which colonic or rectal dysbiosis may exacerbate PO remain hypothetical [31]. Therefore, omics tools for stool analysis appear inappropriate for detection of silent chronic inflammation of the mouth or of the foregut.

Dysbiosis of the foregut may be split into two groups: decreased diversity or overgrowth of undesirable bacteria named small intestinal bacteria overgrowth (SIBO).SIBO usually develops in the ileum, not in the foregut. It can be diagnosed with the detection of hydrogen in exhaled air [32]. 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 [33].

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

Decreased diversity is associated with overweight [34, 35] or inflammatory bowel diseases [36]. Cancer may also be associated with decreased amount of SCFA – attributed to low diversity in the colon [37]. A decrease in diversity - for example after antibiotic therapy – has also been implicated in the attenuation of checkpoint inhibitor efficacy [38].

Less community richness was also observed in the poststroke patients, with consequences on the prognosis [39].

Although causal relationships are not yet established, diversity of the flora should be evaluated and if possible improved as soon as possible.

H2S is a potential marker of gut microbiota alteration [40, 41]. In published studies, the mean H2S levels range from 0.01 ppm [42] to 0.08 ppm in patients with digestive diseases including colorectal cancers [43].

We previously published results within the same range in patients with colonic polyps [44].

In our published observational studies, we asked the patients to hold breath for 20 seconds, which increases the concentration of exhaled gases by at least 30%.

Therefore, the range of results obtained with the device Dräger X-am® 8000 appears compatible with already published data.

In a recent review of literature, exhaled iNO ranges from 0.02 ppm to more than 0.05 ppm when chronic inflammation is expected [45]. It is increased in many inflammatory diseases such as asthma [45], psoriasis [46], heart failure [47] or inflammatory bowel diseases [48].

Since holding breath increases gas concentrations, the range of results obtained with the device Dräger X-am® 8000 appears compatible with already published data.

We therefore suggest that H2S and iNO could reliably be detected with device Dräger X-am® 8000.

H2S works with NO to induce vasodilation and angiogenesis in a cooperative manner [14, 15].

However, chronic inflammation leads to neurotoxic metabolites, decreased serotonin, and a shift towards nitrate/nitrite/NO respiration. High levels of NO can be produced by immune cells and is called inducible-nitric oxide (iNO). Inducible-NO reacts with superoxide, resulting in peroxynitrite formation and cellular toxicity [19]. Exhaled iNO is a recognized marker of allergic diseases [21-23], uncontrolled lupus [24] or progressive cancers [25].

SCFA are mainly produced in the colon. Only tiny amounts of SCFA are produced by the oral flora [49]. SCFA levels can be low and associated with decreased diversity [34, 50]. They can be high and associated with gut dysbiosis, gut permeability, excess adiposity, and cardio-metabolic risk factors [51] or with PO [52]. However, contradictory results have been reported with PO [53]. SCFA measures are therefore difficult to interpret.

Furthermore, measurement of SCFA requires complicated and expensive devices such as Xpid-9500 which cannot be easily implemented in usual practice [54].

The diversity of microbiota of the foregut could be estimated with the exhaled-H2S level. H2S is a gasotransmitter with supposed anti-aging properties and which could significantly reduce progressive, chronic, and degenerative diseases especially, brain, cardiovascular or kidney disease [13]. 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 [55]. This biphasic effect is similar to the one described with NO.

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 [56].

This short observational study confirms that higher iNO levels are associated with high CLP levels while a higher H2S levels - although within the normal range and assume to be associated with diverse flora – is a marker of mild or lack of inflammation.

This work confirms 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 PO.

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

Salivary Clp and Oral Evaluation of Neutrophilic Chronic Inflammation

CLP is mainly synthesized by neutrophils [1] and is a good marker of neutrophil-induced inflammation. Saliva CLP increase is associated with PO [2,3] which is associated with numerous severe pathologies such as cancer [4-9].

Saliva CLP could also be measured to evaluate oral inflammation in rheumatoid arthritis [57], in inflammatory bowel diseases [58], or oral lichen planus [59].

Oral CLP may also be increased in infant with HP infection [60].

Although the thresholds remain to be refined, the salivary CLP could already be recognized as a reliable marker of oral inflammation.

Two previous observational studies identified 750 ui/ml as a possible threshold for severe inflammation and 450 ui/ml as a possible threshold for mild inflammation [3, 12].

PKM2 Detection in Saliva: The Risk of Cancer or Of Neuro-Inflammation

PKM2 detection is only quantitative. There is no published information on any quantitative approach in saliva. There is no evidence that a quantitative measure has a medical interest.

PKM2 can be measured in the saliva and is strongly correlated with oral squamous cell carcinoma progression [61]. PKM2 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 [2, 12]. This measure might be reserved for patients with high levels of CLP in saliva.

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 [11]. PKM2 is a recognized marker of dysplastic polyps of the colon-rectum [62].

HP is associated with an increased risk of non-cardia gastric cancer [63] and PKM2 switch could be involved in gastric cancer development [64].

In this observational study, we found no association between CLP level, PKM2 detection and CMV serology or HP serology.

However, there is a clear association between PKM2 detection and high CLP or iNO levels, or low H2S levels.

We hypothesised that silent chronic inflammation and low H2S are markers of mucosal chronic inflammation associated with predictable atrophy/dysplasia.

We suggest a practical ambulatory approach in any patient with oral or digestive symptoms in order to detect silent chronic inflammation. See figure 1.

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 any patients with PO and abnormal breath test results.

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

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 [2, 12].

Clinical Implications and Future Directions

This work confirms the hypothesis that high salivary CLP is associated with foregut dysbiosis and PKM2 switch.

After breath test, we suggest that salivary CLP could be an adequate pre-screening marker for oral or digestive cancers in patients with PO.

The flow chart depicted in figure 1 is not time consuming, and appears reliable to detect silent chronic inflammation which may spread down-ward or to the brain.

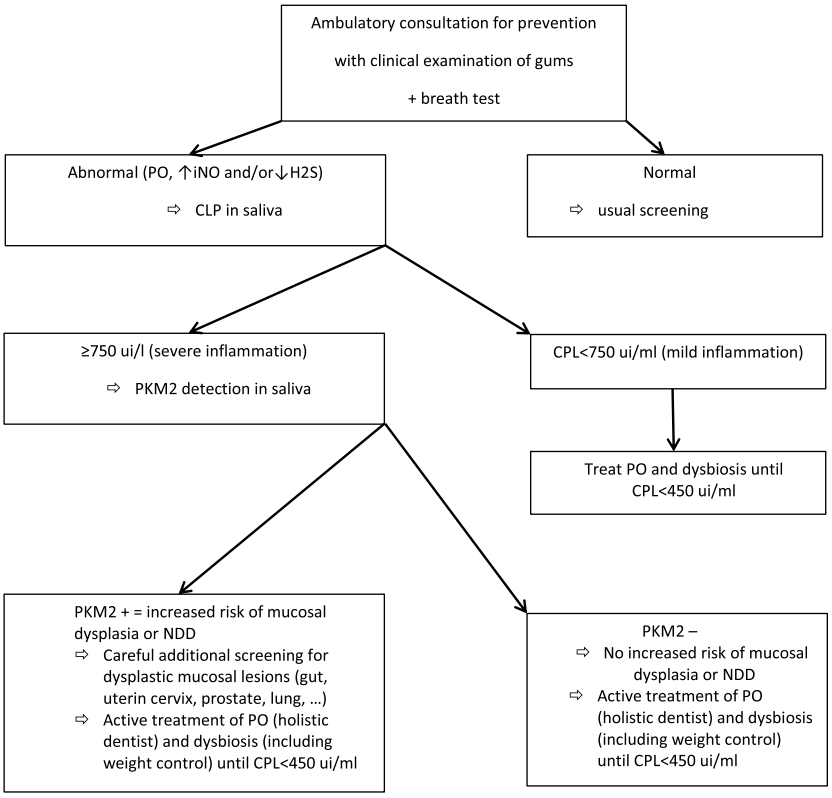

Figure 1: Suggested Algorithm for Early Detection of Mucosal or Brain Chronic Inflammation Based On Breath Test, and CPL or PKM2 Detection in Saliva

Limitations of the Study

The retrospective design of the study precludes any causal relationship conclusion.

All patients were Caucasian which may limit our conclusion to this population.

Populations were not randomized and the groups may be different, leading to some biases. However the demographic data were similar regarding age, body weight, or HP or CMV infections. Therefore the two groups appear similar.

This observational study was performed on a short timeframe. To our knowledge, no publication reports seasonal trends in calprotectin concentrations. However, viral infections or flares of autoimmune diseases, which may increase oral inflammation, are more frequent in winter, early spring or late summer [65]. Therefore, January to June is rather a good period to detect flares

of oral neutrophilic inflammation.Inflammation which is not neutrophilic dependant is not detected by CLP or PKM2.

Exhaled iNO may be a marker for the eosinophilic pathway of chronic inflammation.

Not all comorbidities were documented. However, all causes of severe inflammation were reported. All details are not provided in this article.

Not all medications were documented. However, no patient was treated with corticosteroids, NSAIDS or immunosuppressant therapy (such as TNF antagonists). Therefore, no treatment was expected to have a significant impact on oral inflammation.

Conclusion

We hypothesise that a simple flow chart for early detection of dangerous chronic inflammation of the mouth or of the foregut could be applied in ambulatory medicine. We suggest its application in all patients with oral or digestive symptoms.This early detection is essential as treatments to reduce oral inflammation or its complications are now available.There is currently no recommendation to detect such a chronic inflammation, which could mean a loss of opportunity for a large part of the population.

This work is based on currently available simple and inexpensive devices which may be used in ambulatory consultations. This is more a framework for further investigation and evaluation than a definitive conclusion with fully validated thresholds.

It has the advantage of being immediately applicable in an area where evaluation is sorely lacking despite major potential systemic complications.

Further studies are required to refine the threshold levels for CPL or H2S/NO levels e.g. 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, stomach emptying and body weight, dysplastic mucosal lesions, some cancers, osteoporosis, alveolar bone loss, anxiety-depression episodes, etc.

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