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Salivary Calprotectin is a Marker for Periodontitis, Osteoporosis or Chronic Inflammation of Brain, Joints, Liver or Skin

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Abstract

Background: Calprotectin (CPL) is a marker of neutrophil-induced inflammation.

Objective: Assess whether salivary CPL could be a useful marker of chronic inflammation.

Methods: All relevant data were collected about patients who consulted from 2024 October 20th to December 20th and who had a previous medical history of periodontitis (PO).Patients were classified according to the level of salivary CPL. The CPL threshold for active PO and/or Fusobacterium nucleatum + Porphyromonas gingivalis (Fn+Pg) on dental collets was determined. Patients with PO remission, without Fn+Pg on dental collets and below the identified threshold were attributed to group A. Other patients were attributed to group B. Both groups were compared.

Results: 114 patients were included: 99 in group B and 15 in group A. Salivary CPL ranged from 191 µg/g to >1000 µg/g. The cut-off value between the two groups was equal to 450 µg/g.Patients in group B present more frequently with osteoporosis, or brain, joints, liver or skin chronic inflammation ($p<0.001$). A possible association ($p<0.01$) is also noted with an altered gut flora, fatty liver, hypotonia of the foregut and Ig CMV+ serology. Surprisingly, other inflammatory parameters and prediabetes were not associated with group B.

Conclusion: Salivary CPL level is an interesting parameter to evaluate the inflammation of the upper part of the body, including mouth, brain, joint, liver and skin.

Keywords: Calprotectin; Periodontitis; Osteoporosis; Brain; CMV

List of Abbreviations: BMI: Body Mass Index; C. Acnes: *Cutibacterium Acnes*; CLP: Calprotectin; CMV: Cytomegalovirus; Fn: *Fusobacterium Nucleatum*; HPV: Human Papillomavirus; HSV: Herpes Simplex Virus; MLR: Monocyte/Lymphocyte Ratio; NRL: Neutrophil/Lymphocyte Ratio; PDL1: Programmed Death-Ligand 1; PLR: Platelet/Lymphocyte Ratio; Pg: *Porphyromonas Gingivalis*; PO: Periodontitis; SIBO: Small Intestinal Bacterial Overgrowth

Introduction

Salivary proteins - such as IL1β, IL6, IL8 or TNF-α - can be used as inflammatory markers of the oral cavity [1,2]. However none of them can be measured by a simple inexpensive ambulatory test. We therefore decided to use a low-cost CLP kit for all outpatients with a history of PO. CLP is mainly synthesized by neutrophils [3] and is a good marker of neutrophil-induced inflammation, particularly used in the monitoring of inflammatory bowel diseases [4].

Faecal CLP increase has been associated with numerous and diverse diseases such as neurodegenerative diseases [5,6], autoimmune diseases [7], digestive cancers [8], eosinophilic gastrointestinal diseases [9], liver steatosis [10], or food intolerance [11], etc..Saliva CLP is increased in patients with PO [12,13], Sjögren syndrome [14] or post-menopausal osteoporosis [15].

PO is very common [16] and – like CLP increase – is associated with many severe pathologies such as cancer [17], metabolic syndrome [18], as well as brain [19], cardiovascular [20], joints [21], bone [22] or skin inflammation [23]. Oral bacteria and viruses have been implicated in the occurrence of PO or endodontic lesions, especially *Fusobacterium nucleatum* (Fn) and *Porphyromonas gingivalis* (Pg) [24] or herpes viruses [25,26].

PO and endodontic lesions are entangled [27]. *Cutibacterium acnes* (C. acnes) is the main bacteria found in endodontic infections [28] or in periodontal abscess [29]. Consequently, endodontic therapy is referred to improve gum's healing [30].

Severe PO is associated with an increased NLR which depicts its inflammatory and destructive nature [31]. However, a relevant marker is not currently available in usual practice to quantify mild to severe inflammation.Currently, Outpatient kits for CLP dosage are available, which could greatly simplify the monitoring of chronic inflammatory diseases or could allow better planning of dental or gingival aggressive treatments by postponing their execution outside the inflammatory phase.

We investigated whether an Outpatient kit for CLP dosage could be of interest to evaluate the inflammation of the upper part of the body, including mouth, brain, joints, liver and skin.

We also investigated whether salivary CLP was associated with PO, oral dysbiosis (e.g. Fn+Pg on dental collets or C. acnes on the tongue), signs of increased visceral fat (e.g. liver steatosis, pancreatic steatosis, prediabetes, foregut hypotonia, altered gut microbiota) or biological inflammatory marker/ratios (e.g. increased CRP, NLR, MLR, PLR).

Material and Methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bacterial Overgrowth (SIBO), from 2024 October 20th to December 20th.There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before data collection. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE). French legislation does not require the consent of an Institutional Review Board in such epidemiological studies.

Inclusion Criteria

All patients with a previous 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, BMI, osteoporosis, CMV-serology, glycaemia, NLR, MLR, PLR, oral CLP level, clinical signs of PO, Fn+Pg on dental collets, C. acnes on the tongue, adequate oral hygiene, medical history of herpetic flare, medical history of zona, HPV infection, chronic inflammation including anxiety/depression, brain fog, burnout, chronic fatigue syndrome, long COVID, memory loss or Parkinson, altered flora (breath test), psoriasis, arthritis, autoimmune disease, liver steatosis or hypotonia of the foregut (transabdominal ultrasound).Patients with uncontrolled diseases (e.g. severe sepsis, autoimmune disease, cancer, *diabetes mellitus*, renal or hepatic insufficiency, endocrine disorders, hypertension, and cardiac failure) were excluded.

Dosage of Salivary CLP

BÜLMANN Laboratories AG (Schönenbuch, Switzerland) currently commercializes a kit to measure faecal CLP. We used this device (IB*Doc*®) outside of its indication for off-label measure of salivary CLP. We replaced the 60 µg of stool with 0.5 ml of saliva.

Gas Measurement

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

Exhaled gazes from the second bag are then immediately measured by the X-pid 9500®, an ambulatory gas chromatograph associated with photoionization detection technology [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors]. X-pid 9500® detects volatile organic compounds concentrations as low as 50 ppb.

Acetic acid is detected between 4.4 to 4.7 seconds, propionic acid is detected between 4.7 to 5.0 seconds and butyric acid is detected between 7.8 to 8.1 seconds.

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

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am® 8000 [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results are published separately.

Both devices are easily portable and equipped with powerful pumps. The setup is basic and similar for both devices. It requires only a short neutral tube to connect the bag and the device.Altered microbiota was diagnosed when SIBO or poor diversity (low level of volatile organic compounds) was detected.

Ultrasound Examination

Gastroparesis was diagnosed when the surface of the stomach reached 10 cm^2 after 10 hours of fasting. Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileocecal junction. Lack of gastro-duodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic abdominal manoeuvers. Jejunal hypotonia could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is visualized [32]. Abdominal ultrasound examination also enables to diagnose liver steatosis.

Oral Examination

Fn+Pg of dental collets

Fn fluorescence interacts with Pg when excited with 405-nm blue light. Green fluorescence of Fn changes to red fluorescence in the presence of Pg [33]. Therefore, the presence of red lines at the dental collets enables to identify biofilms containing Fn+Pg.

C. acnes on the tongue

C. acnes produces porphyrins, which exhibit fluorescence properties and colour bacteria a bright red-orange under the light of a Wood's lamp [34]. Therefore, the presence of bright red-orange on the tongue identifies biofilms containing C. acnes.

Statistics

No case was discarded except when at least one exclusion criteria was identified. As a consequence no recruitment or selection bias is expected. All patients were Caucasian.

Comparisons of percentages or means used two-sample t-tests. Yates correction was used for small samples.

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

Identified statistical differences only concern few percentages. We therefore did not calculate confidence intervals and effect sizes which require means and standard deviations. It is therefore not possible to provide a clear understanding of the magnitude of the observed relationships.

Results

This descriptive observational epidemiological study includes 114 patients. No patient was excluded since all required data were available. There is therefore, no exclusion effect.

Determination of the Threshold of Salivary CLP (See Table 1)

Patients were classified according to CLP levels.

The first 15 patients (from 191 to 448 µg/g) did not present with PO or Fn+Pg (group A).

Patients from 792 to >1000 µg/g, always present with PO and Fn+Pg (subgroup B2).

From 458 to 788 µg/g, patients present with PO and/or Fn+Pg in 57.5% of cases, despite 65.8% of adequate oral hygiene (group subB1).

We concluded that CLP below 450 was associated with low inflammation, CLP >790 was associated with severe inflammation and CLP from 450 to 790 was associated with medium inflammation.

According to the protocol we compared the 15 patients of the first group (group A) to the 99 remaining patients (group B).

Despite a similar oral hygiene rate, PO and/or Fn+Pg was significantly higher in group B than in group A.

Group B is perhaps inhomogeneous since there are trends of statistical differences (p<0.01) between subgroup B1 and subgroup B2 regarding the frequency of PO and/or Fn+Pg, and of oral hygiene.

We speculated that bad oral hygiene (only 34.6% in sub group B2 versus 65.8% in subgroup B1) could have worsened local inflammation and had therefore increased CLP levels.

Table 1: Patients classified according to salivary CLP concentrations, PO and/or Fn+Pg, or adequate oral hygiene

	Salivary CLP levels in µg/g	PO and/or Fn+Pg% of patients	Adequate oral hygiene% of patients
Patients 1 to 15 15 patients (in group A)	From 191 to 448	0%	46.7%
Patients 16 to 88 (subgroup B1) 63 patients (in group B)	From 458 to 788	57.5%	65.8%
Patients 88 to 114 (subgroup B2) 26 patients (in group B)	From 792 to >1000	100%	34.6%
P values between A and B1		**<0.001**	>0.05
P values between B1 and B2		**<0.01**	**<0.01**

Comparison of Group A and B (See Tables 2 and 3)

Groups A and B were similar according to gender, age and Body Mass Index (BMI), adequate oral hygiene, herpetic flares, zona, or medical history of papillomavirus (HPV). See table 2.

The two groups were also similar regarding prediabetes, C. acnes, or CRP, NLR, PLR and MLR.

As expected from the study protocol, the two groups were statistically different regarding PO and/or Fn+Pg (<0.001).The percentage of osteoporosis, of ongoing joints, liver, skin chronic inflammation, or of anxiety/depression, brain fog, burnout, chronic fatigue syndrome, long COVID, memory loss, or Parkinson (see tables 2 and 3) were higher in group B (p<0.001).

A difference between Group A and Group B regarding CMV+ IgG and metabolic syndrome (e.g. altered gut microbiota, liver steatosis and foregut hypotonia) is possible although it was not statistically confirmed due to lack of study power. A trend was however evidenced (p<0.01).

We concluded firstly that salivary CLP is associated with bone, brain, joints, liver and skin chronic inflammation, and is a better marker than CRP, NLR, PLR or MLR. Secondly that CMV infection and metabolic syndrome may be relevant markers to investigate in patients with PO and/or Fn+Pg.

Table 2: Demographic and clinical data between group A (less than 450 µg/g) and group B (more than 450 µg/g)

	Gender (% of female)	Age (years)	BMI	PO and/orFn+Pg	Adequate oral hygiene	Medical history				
						Ongoing joints, liver, mouth, or skin chronic inflammation*	Anxiety/depression, brain fog, burn-out, chronic fatigue syndrome, long COVID, memory loss, Parkinson	Herpes simplex	zona	HPV
Group A 15 cases	80,0%	53.2 +/-14.3	21.0 +/- 2.4	0	46.7%	0	0	33.3%	6.7%	6.7%
Group B 99 cases	78.80%	54.9 +/- 13.6	19.8 +/- 5.4	69.9%	51.0%	46.6%	20.2%	35.4%	10.0%	10.0%
P value	>0.05	>0.05	>0.05	**<0.001**	>0.05	**<0.001**	**<0.001**	>0.05	>0.05	>0.05

* cholangitis, chronic endodontic infections, juvenile arthritis, lichen, MASH, multiple sclerosis, psoriasis, rheumatoid arthritis, scleroderma, Sjögren syndrome, systemic lupus erythematous, spondylarthrosis, vitiligo.

Table 3: Biological and radiological data between group A (less than 450 µg/g) and group B (more than 450 µg/g)

	Prediabetesglycaemia>1.1g/l	IgG CMV+	CRP	NLR	PLR	MLR	altered gut flora (breath test)	Liver steatosis	Foregut hypotonia	Osteoporosis	C. acnes of the tongue
Group A 15 cases	33.3%	20.0%	1.7 +/- 0.3	1.9 +/- 0.9	121 +/- 33	0.26 +/- 0.13	13.3%	6.7%	20.0%	0	33.3%
Group B 99 cases	20.2%	57.6%	1.8 +/- 1.3	1.7 +/- 0.8	150+/-53	0.34 +/- 0.08	53.5%	24.2%	61.6%	26.3%	29.3%
P value	<0.05	**<0.01**	>0.05	>0.05	>0.05	>0.05	**<0.01**	**<0.01**	**<0.01**	**<0.001**	>0.05

Discussion

Salivary CLP can be quantitatively evaluated by the Outpatient kit provided by BÜHLMANN Laboratories AG. The level ranked from 191µg/g to more than 1000µg/g. To our knowledge, this is the first time such a kit has been used for saliva.

Patients with level of salivary CLP lower than 450 µg/g did not present with PO or Fn+Pg. We therefore considered that such a low CLP level should be the goal to be achieved before claiming that oral inflammation is controlled. It may also be a pre-requisite for dentists considering dental implants with or without bone grafting, as chronic inflammation appears to be associated with osteoporosis and can therefore hinder bone reconstruction.

Outpatient Kit of CLP May Help to Screen, Diagnose and Follow Chronic Inflammation, Better Than Other Available Criteria

CLP is produced by neutrophils [3] and is a recognized marker of bowel inflammation [4].Saliva CLP increase is associated with PO and chronic inflammation [12-15]. PO is associated with many severe diseases [17-23] and abundant data suggest a causal cross-role of Fn, Pg, C.acnes and herpes viruses [24-25].

Animal models have confirmed the causal role of periodontal pathogens in brain inflammation [35-37].

This work confirms that high salivary CLP is associated with PO, periodontal pathogens as well as bone, brain, joints, liver and skin chronic inflammation. A trend for statistical relationship was found with Ig CMV+ serology, however not with herpetic flare, zona or HPV. We concluded that bacteria are more implicated in neutrophilic- induced inflammation than herpetic viruses.

However viral infections have been reported to increase oral inflammatory diseases like periodontitis, endodontic disease, and peri-implantitis [38]. A cross-talk, synergy or association of pathogens is likely [39]. CMV could be the most deleterious virus.

In this work salivary CLP appears to be more reliable than systemic markers such as CRP, NLR, MLP or PLR.

In patients with COVID-19, serum CLP on admission was the only independent risk factor for intubation/death even after adjustment for age, sex, body mass index, comorbidities, neutrophils, lymphocytes, neutrophil to lymphocytes ratio, ferritin or CRP [40].

Serum CLP could also be good marker of persisting viral activity in COVID-19, which enable to discriminate between disease activity and recovery [41]. Increased CLP could connect ongoing viral infection with neutrophilic inflammation [42].

COVID-19 severity correlates with serum CLP level or PD-L1 expression. Critical COVID-19 seems to be characterized by an immune profile of activated and exhausted T cells and monocytes. This immune phenotype may influence the capacity to mount an efficient T-cell immune response. Plasma B-cell activity and CPL were higher in critical COVID-19 while most transcripts related to immune functions were reduced [43].

Such a mechanism may explain why severe COVID-19 may trigger PO and vice-versa [44]. This bidirectional mechanism mainly based on CLP and PDL1 expression may explain why other markers were not increased in the group B despite clinical periodontitis.

According to a recent meta-analysis, NLR, MLR and PLR could be rather indicative of cancer risk [45,46].

NLP increase associated with PO severity could therefore be a spurious effect of dysbiosis shared by the mouth, the stomach and the colon which simultaneously promotes PO, as well as the risk of gastric or colonic cancers.

Salivary CLP, Altered Gut Microbiota, Liver Steatosis and Foregut Hypotonia

Altered diversity of the gut microbiota is associated with metabolic syndrome [47] and PO [48].

Foregut hypotonia (mainly gastric and jejunal) is mainly found in patients with severe liver steatosis [32].

Liver steatosis is the corner-stone of metabolic syndrome [49]. It is therefore not surprising to find a trend between high salivary CLP and liver steatosis or altered diversity of gut microbiota.

CLP in gingivo-crevicular fluid is increased in patients with coronary disease [12], arrhythmia or decreased left cardiac function [50].

Our results are coherent with increased cardiac or metabolic risks in patients with elevated salivary CLP.

Prediabetes (none of our patient presented with diabetes or uncontrolled diabetes) does not appear to have any influence on salivary CLP levels.

Should Salivary CLP Tests Be Introduced in Routine to Detect Patients at Risk of Certain Cancers or to Optimize Dental Surgery ?

Aggressive oral microbiota is associated with the development of tumours in distant organs [51]. We therefore suggest that salivary CLP could be an adequate pre-screening marker for oral or digestive cancers.

CLP dosage distinguishes healthy periodontium and PO [5]. It also helps to diagnose peri-implantitis [52]. Salivary CLP dosage could therefore be useful to monitor dentals surgical procedures.

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 two groups may be different, leading to some biases. However the demographic data were similar as well as glycaemia, CRP, NLR, MLR, PLR, herpetic flare, zona, HPV infection, and oral hygiene. All patients with uncontrolled sepsis were excluded.Therefore the two groups appear similar except with regards to CLP, PO and/or Fn+Pg, and factors which may influence these conditions.

This observational study was performed on a short timeframe and only in autumn.

To our knowledge, no publication reports seasonal trends in calprotectin concentrations.

However, PO severity may be alleviated by vitamin D or lycopene [53,54].

On the contrary, viral infections or flares of autoimmune diseases, that may increase oral inflammation, are more frequent in winter, early spring or late summer [55].

Vitamin D is synthetized after sun exposure. Lycopene is found in reddish vegetables. So one can expect that autumn is rather a period with adequate vitamin D and lycopene levels. In addition, fewer viral infections or autoimmune outbreaks occur in the fall. In a shell nut autumn appears to be the best period to confirm the lack of oral inflammation.

Application of This New Knowledge For Routine Practice

Quantitative testing of salivary CLP with the Outpatient kit of BÜHLMANN Laboratories AG is easy to perform, reliable, inexpensive and useful to detect chronic inflammation. Salivary CLP appears to be an independent marker, not redundant with those currently available.

Since CLP and PO are probably cross-linked and associated with numerous severe disease such as cancers, cardiovascular diseases, liver steatosis, neurodegenerative diseases, autoimmunity or osteoporosis, we suggest that salivary CLP should be mea-

sured in all patients with PO or chronic inflammation. It may also be performed in patients who should undergo dentals surgical procedure in order to select the optimal period for mucosal and bone regeneration.This test could also be appropriate for all patients interested with antiaging since chronic inflammation is associated with oxidative stress and aging.

Such prevention may also reduce diseases promoted by viral infections, including COVID-19.

Conclusion

Quantitative CLP assay designed to be used in an ambulatory setting could be proposed for the detection, prevention and monitoring of chronic inflammation associated with many serious diseases currently uncontrolled. It could also be used by dentists before any reconstructive surgery.

However, further studies are required to refine the threshold levels for CPL, e.g. according to the age, underlying conditions or perhaps the season.

Long-term observational studies could assess the value of reducing salivary calprotectin through local care and see its preventive effect on osteoporosis, alveolar bone loss, certain cancers, anxiety-depression episodes, etc.

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