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Salivary Calprotectin and Pyruvate Kinase M2 Are Markers for Mucosal Dysplastic Lesions, Multiple Sclerosis or Parkinson Disease

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Abstract

Background: Calprotectin (CPL) is a marker of neutrophil-induced inflammation and pyruvate kinase M2 (PKM2) is a marker of cancer.

Objective: Assess whether the addition of PKM2 detection to the measurement of CPL in saliva could improve the detection of cancer or severe chronic inflammation.

Methods: All relevant data were collected about 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 (group 1 >790 ui/ml and group 2 ≤790 ui/ml) and to the detection of PKM2 in saliva (group A positive for PKM2, group B negative for PKM2). Groups (A1, A2, B1, B2) were compared according to on-going diseases, cytomegalovirus (CMV) serology or herpetic flares.

Results: 112 patients were included: 36 in group 1, 76 in group 2, 28 in group A and 84 in group B. All patients positive for CPL and PKM2 (group A1) had a recent medical history of colorectal polyps, mucosal dysplasia (cervical dysplasia due to papillomavirus or gastric dysplasia) or central nervous system diseases (multiple sclerosis or Parkinson's disease). Patients negative for these markers (B2) did not present with any of these conditions ($p<0.001$). The double negative patients present with a higher frequency of severe cardiovascular disease in comparison with the pooled three other groups (11.9% versus 0%; $p<0.001$).

Conclusion: Adding PKM2 detection to salivary CPL level increases the sensitivity and the negative predictive value for the detection of cancer or ongoing central nervous system inflammation. It is not relevant for the detection of severe cardiovascular inflammation.

Keywords: Calprotectin; PKM2; Cancer; Brain; CMV

List of abbreviations: CLP: calprotectin; CMV: cytomegalovirus; Fn: *Fusobacterium nucleatum*; HPV: Human Papillomavirus; HSV: herpes simplex virus; MS: multiple sclerosis; NPV: Negative predictive values; PD: Parkinson disease; Pg: *Porphyromonas gingivalis*; PKM2: Pyruvate kinase M2; PPV: Positive predictive values; PO: periodontitis; Se: Sensitivity; Sp: Specificity.

Introduction

Salivary proteins - such as IL1β, IL6, IL8 or TNF-α - can be used as inflammatory markers of the oral cavity [1]. However, CLP is the only one simple and inexpensive test which can be used in ambulatory medicine [2, 3].

CLP is mainly synthesized by neutrophils [2] and is a good marker of neutrophil-induced inflammation, particularly used in the monitoring of inflammatory bowel diseases [4].

Saliva CLP is increased in patients with PO [5] which is associated with severe pathologies such as cancer [6], metabolic syndrome [7], psoriasis [8] as well as bone loss [9], or brain [10], cardiovascular [11], or joints inflammation [12].

PKM2 can play an important role in tumour cell energy supply, epithelial-mesenchymal transition, invasion, metastasis, and cell proliferation [13]. Dysplastic colonic or rectal polyps should be sought when PKM2 is detected in stools [14, 15].It can also be measured in the saliva and is strongly correlated with oral squamous cell carcinoma progression [16].

We investigate whether the detection of PKM2 added to the measurement of CLP in saliva may improve the detection of an increased risk of mucosal dysplasia.

We take the opportunity of this observational study to include patients with other types of chronic inflammation such as severe vascular diseases or severe neuro-inflammation. Sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) are calculated to test firstly the interest of adding PKM2 detection and secondly the reliability of these combined two markers regarding detection of chronic inflammation or cancer.

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, 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, 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, weight, height, CMV-serology, oral CLP or PKM2 level, clinical signs of PO, medical history of herpetic flare, medical history of zona, HPV infection, long COVID, multiple sclerosis (MS), memory loss or Parkinson disease (PD), psoriasis, arthritis, autoimmune disease, mastocyte activation syndrome, any chronic inflammation including severe anxiety/depression or severe arterial disease. All this information should be available.

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. Yates correction was applied for small samples.

For very small samples we used the Poisson's distribution.

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.

Limitations of the study

All inflammatory diseases were documented. However, confounding factors are possible. For example ongoing treatments for periodontitis, multiple sclerosis, Parkinson's disease, diabetes type 2 or cardiovascular diseases were not 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.

No case was discarded after inclusion. As a consequence no recruitment or selection bias is expected. All patients were Caucasian. Our conclusions may therefore be limited to a Caucasian population.

Results

This descriptive observational epidemiological study includes 112 patients. No patient was excluded since all required data were available. There is therefore, no exclusion effect.

Patients of groupA1 (double positive patients) might be older than others patients (trend; p<0.01): approximately 8 years of age. The CMV serology might be more frequently positive in groupA1 than in groupB2 (double negative patients): 66.6 versus 35.8% (p<0.01, trend). These two parameters may have an incidence on immunity and therefore on the occurrence of dysplastic mucosal lesions or cancer. Other parameters were similar between groups. (see table 1)

Table 1: Demographic data according to the four groups. The number of patients is in parenthesis. No statistical significant difference was found between groups except a trend for age and for CMV serology between A1 and B2.

	Gender (% of female)	Age	Weight	Height	CMV serology(% positive)	Herpetic flare or zona	Osteoporosis(% positive)
Group A1 Double positive (19)	72.2	63.0 +/- 9.9	63.1 +/- 11.2	168.3 +/- 6.1	66.6	27.8	55.5
Group A2 (PKM2+) (9)	77.8	56.2 +/- 15.2	63.2 +/- 16.3	167.1 +/- 8.4	33.3	33.3	44.4
Group B1 (CPL>790) (17)	82.4	55.7 +/- 11.3	60.3 +/- 13.2	164.5 +/- 9.9	47.1	41.1	52.9
Group B2 Double negative(67)	71.6	54.9 +/- 13.4	64.3 +/- 15.0	167.4 +/- 10.3	35.8	49.2	43.3
P values A1 versus B2	NS	<0.01	NS	NS	<0.01	NS	NS

Comparison of Groups

Patients with a recent medical history of pancreatic cancer, or of dysplastic mucosal lesion of the colon-rectum, uterine cervix or stomach belong more frequently to the group A1 or B1 than to other groups (p<0.001).Isolated detection of PKM2 is rare (9 cases among 112 patients) while isolated CPL increase or double positive test were frequent (19 +17 cases).

We concluded that CPL dosage is always necessary to evaluate oral inflammation, while PKM2 detection should probably be restricted to patients with high CPL levels.MS or PD appears to be related to groupA1. One of the two patients with PD from groupA1 and one of the two patients with MS from group A1 were CMV+.

Patients in groupA1 present more frequently with psoriasis than patients in groupB1 (CPL increase alone), p<0.001. Double positive patients might be more exposed to psoriasis than double negative patients (28% in groupA1 versus 13% in group B2, p<0.01, trend).

We concluded that the association of CPL with PKM2 may also be appropriate to detect such diseases or confirm that they are explained by neutrophilic-dependant inflammation and PKM2 switch.

Severe arterial diseases were inversely correlated with CPL level or positive PKM2+high CPL level. These tests were therefore inappropriate to detect such diseases.We hypothesize that the immunological pathogenesis of these two kinds of diseases are different. For example high CPL is known to be related to neutrophilic-dependant inflammation which could be associated with dysplastic mucosal lesion or MS/PD. On the contrary severe arterial lesion could have an eosinophilic or lymphocytic origin which is usually not associated with neutrophils or CPL increase.

For other diseases (severe anxiety/depression, rheumatoid arthritis, systemic lupus, ongoing however controlled breast cancer, mastocyte activation syndrome, dental abscess) the limited number of cases precludes any relevant analysis and conclusion. (Table 3)

Table 2: Recent medical history (<4 years) or underlying diseases according to the four groups. The number of cases is provided, not percentages. One patient may present with several diseases. Diseases with statistical differences between groups.

	Cancer or dysplasticgastric, pancreatic or colorectal lesion	Uterine cervical dysplasia(HPV+)	MS or Parkinson	Severe arterial disease (aortic coronary or carotid artery)Controlled	Psoriasis
Group A1 (19) CPL>790 and PKM2+	12	4	4	0	5
Group A2 (9) PKM2+	1	4	0	0	2
Group B1 (17) CPL>790	6	2	1	0	2
Group B2 (67) CPL<790 and PKM2-	2	0	0	5	9
P values A1 versus B2 A2 versus B2 B1 versus B2 A1 versus A2 A1 versus B1 A2 versus B1 B1 versus B2	<0.001 <0.001 <0.001 <0.01 NS NS <0.001	<0.001 <0.001 <0.001 NS NS <0.01 <0.001	<0.001* NA † NA NA NA NA NA	<0.001 <0.001 <0.001 NA NA NA <0.001	<0.01 NS NS NS <0.001 NS NS

*p is >0.05 when MS and PD are considered separately

† Not applicable: The limited number of cases precludes any relevant statistical analysis

Table 3: Recent medical history (<4 years) or underlying diseases according to the four groups. The number of cases is provided, not percentages. One patient may present with several diseases. Diseases without statistical differences between groups.

	Severe depressiontreated	Rheumatoid arthritistreated	Systemic lupustreated	Breast cancerbeingtreated	Mastocyte activation syndrome	Dental abscess to be treated
Group A1 (19) CPL>790 and PKM2+	0	0	0	0	1	0
Group A2 (9) PKM2+	1	1	0	2	1	1
Group B1 (17) CPL>790	0	0	0	2	1	1

Group B2 (67) CPL<790 and PKM2-	3	3	2	2	2	2
P values	A1 versus B2 ; A2 versus B2 ; B1 versus B2 ; A1 versus A2 ; A1 versus B1 ; A2 versus B1 ; B1 versus B2 : Not applicable. The limited number of cases precludes any relevant statistical analysis					

§ Se=a/(a+c); Sp=d/(b+d); PPV=(Se*prevalence)/(Se*prevalence+(1-prevalence)*(1-Sp)); NPV=Sp*(1-prevalence)/(Sp*(1-prevalence)+prevalence*(1-Se)); prevalence=(a+c)/(a+b+c+d)

Determination of sensitivity, specificity, VPP, NPV

The sensitivity and the NPV of salivary calprotectin level alone were respectively equal to 69% and 86% for dysplastic mucosal lesions and to 81% and 91% for dysplastic mucosal lesions or MS/PD. (table 4)

The sensitivity and the NPV of salivary calprotectin level associated with PKM2 detection were respectively equal to 84% and 96% for dysplastic mucosal lesions and to 100% and 100% for dysplastic mucosal lesions or MS/PD. (table 5)

We concluded that the detection of PKM2 added to the measurement of CPL improves the sensitivity and the NPV of CPL alone for the detection of mucosal and MS/PD.

Table 4: Sensitivity (Se), Specificity (Sp), Positive predictive values (PPV) and Negative predictive values (NPV) of CLP level alone.

		Number of patients	Groups A1 and B1	Groups A2 and B2	Se§SpPPVNPV
Dysplastic mucosal lesion	Yes	32	25	7	69%91%78%86%
	No	80	11	69	
Dysplastic mucosal lesions or MS/PD	Yes	31	29	2	81%97%94%91%
	No	81	7	74	

§ Se=a/(a+c); Sp=d/(b+d); PPV=(Se*prevalence)/(Se*prevalence+(1-prevalence)*(1-Sp));NPV=Sp*(1-prevalence)/(Sp*(1-prevalence)+prevalence*(1-Se)); prevalence=(a+c)/(a+b+c+d)

Table 5: Sensitivity (Se), Specificity (Sp), Positive predictive values (PPV) and Negative predictive values (NPV) of CLP level+PKM2 detection.

		Number of patients	Group A1Double +	Other groups	Se§SpPPVNPV
Dysplastic mucosal lesion	Yes	31	16	15	84%84%52%96%
	No	81	3	78	
Dysplastic mucosal lesions or MS/PD	Yes	31	19	12	100%87%61%100%
	No	81	0	81	

§ Se=a/(a+c); Sp=d/(b+d); PPV=(Se*prevalence)/(Se*prevalence+(1-prevalence)*(1-Sp));NPV=Sp*(1-prevalence)/(Sp*(1-prevalence)+prevalence*(1-Se)); prevalence=(a+c)/(a+b+c+d)

Discussion

Chronic inflammation; CLP; PKM2; neutrophil-eosinophil balance

CLP is produced by neutrophils [2] and is a well-established marker of bowel inflammation [4]. Saliva CLP increase is associated with PO [5] which is associated with chronic inflammation and many severe diseases [6-12].

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. [13] PKM2 is a recognized marker of dysplastic polyps of the colon-rectum [14, 15] and may be detected in stools by an ambulatory device commercialized by Schebo AG.

CMV chronic infection could increase the expression of PKM2 [16].

Patients with MS present with elevated neutrophil counts in the acute phase, whereas the lymphocyte and eosinophil counts does not differ from healthy control [17, 18].

Patients with PD also present with high neutrophil-lymphocyte ratio [19] or high CLP level in serum or stools [20, 21].

At least in the early phase of psoriasis, neutrophils infiltrate the skin and release neutrophils extracellular traps, exosomes, metalloproteinase 9, and IL-17 [22].

At a later stage, natural Th17 cells are recruited and maintain or exacerbate psoriasis [23].

Eosinophils are rare in psoriasis and are not expected to be involved [24].

In psoriasis, PKM2 is upregulated and promotes keratinocyte proliferation through the IL17 pathway [25, 26].

The neutrophil-lymphocyte ratio is a documented marker of global cardiovascular disease [27], arterial stiffness [28] or carotid plaque vulnerability [29].

Serum CLP is clearly associated in the prediction of mortality from ischemic stroke [30]. Serum CPL is also a marker for aortic aneurysm [31] or coronary disease [32].

Current available data suggest that neutrophils are implicated in the acute phase, while eosinophils are promoting atherosclerosis, calcification or dissection [33, 34].

Eosinophils appear to be protective of thrombosis and are therefore associated with other types of arterial diseases than neutrophils [35, 36].

Taking inspiration from the asthma model, the neutrophilic phenotype depends on IL17 while the eosinophilic phenotype depends on TH2 mediators [37, 38].

These two immunologic pathways appear to be mutually exclusive.

The modification of eosinophil count may predict the switch to the neutrophilic phase and therefore may point out the high risk of acute complications, e.g. myocardial infarction [39].

Serum calprotectin is therefore a marker of impaired endothelial integrity, diminished nitric oxide production, and fostered en-

dothelial mesenchymal transition, figuring impending complication of atherosclerosis [40].

In this observational study

To our knowledge, it is the first time that the Schebo test is used for PKM2 detection in saliva, especially in combination with CPL.

This work confirms that high salivary CLP is associated with consequences of chronic mucosal inflammation [3] such as dysplastic lesions of gut or uterine cervix. It also appeared that severe oral inflammation is associated with MS or PD.

To our knowledge, an increased level of CPL or of PKM2 in saliva has never been reported in PD, in MS, or in psoriasis despite the neutrophilic origin of inflammation in these diseases.

We hypothesize that CPL increase and the switch of PKM2 are concomitant and belong to the same inflammatory process which favours the occurrence of severe endothelial, skin or mucosal inflammation leading to dysplasia, psoriasis or brain inflammation.

We also conclude that the use of PKM2 test in saliva improves the sensibility and the PPV of CPL for the detection of dysplastic mucosal lesion or MS/PD.

The group A1 presents with a higher percentage of positive CMV-serology.Interestingly, CMV infection is expected to decrease the risk of PD [41] or of MS [42]. In this short observational study one the two patients with PD from groupA1 was CMV+ and one of the two patients with MS from group A1 was CMV+. The limited number of cases precludes any further analysis.Since CMV favours PKM2 switch and since high CLP level is associated with an increased prevalence of CMV IgG positivity [3], we suggest titrating the antibodies against CMV in all patients with severe periodontitis, especially in those with thyroid nodules who may be at increased risk of cancer [43].

In this short observational study, silent or stabilised treated severe arterial diseases were inversely associated with CPL and PKM2 switch. CPL and PKM2 identify a neutrophilic inflammation. Since severe arterial diseases are reportedly dependent on eosinophils, our results are consistent with the theory of inflammation which separates the two types of inflammation into two exclusive pathways.

Clinical implications and future directions

Aggressive oral microbiota is associated with the development of tumours in distant organs [44]. We therefore suggest that salivary CLP could be an adequate pre-screening marker for oral or digestive cancers in patients with PO and *Fusobacterium nucleatum/Porphyromonas gingivalis* [3].

PKM2 dosage could be added in patients with CPL>790 ui/ml. This assay can be performed from the same sample.

Quantitative dosage of salivary CLP with the Outpatient kit of Bühlmann laboratories AG is easy to perform, reliable, inexpensive and useful to detect chronic inflammation [3].The addition of PKM2 detection to CLP measurement increases the sensitivity and the PPV. The detection is focussed on neutrophilic dependant disease (cancer, some neurologic disease, however not arterial diseases).

We suggest that salivary CLP should at least be measured in all patients with PO or chronic inflammation.

The detection of CLP and, if necessary of PKM2, could also be tested in the early stages of other diseases associated with neu-

trophilic inflammation such as obesity-related diseases or chronic obstructive pulmonary disease [46].

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. For example, the patients of group A1 were older than others and have a higher percentage of CMV serology. However the demographic data were similar regarding, herpetic flares or zona, or osteoporosis which is respectively good markers of antiviral immunity or vagal dystonia associated with CPL level [3].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 [48]. Therefore, January to June is rather a good period to detect flares of oral neutrophilic inflammation.Inflammation which is not neutrophilic dependant is, according to this work, not detected by CLP or PKM2. Biological markers are not yet available to detect non-neutrophilic pathways.

Not all comorbidities were documented. However, all causes of severe inflammation were reported.

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

Quantitative CLP assay with an ambulatory kit is now available and could be widely used for the detection, prevention and monitoring of chronic inflammation associated with many serious diseases currently uncontrolled.

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

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 dysplastic mucosal lesions, certain cancers, osteoporosis, alveolar bone loss, anxiety-depression episodes, etc.

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