UDC 616.717.1
DOI – https://doi.org/10.14300/mnnc.2022.17054
ISSN – 2073-8137

BIOMARKERS AND PROGNOSTIC POTENTIAL OF ORAL FLUID FOR EARLY DIAGNOSIS OF CHRONIC PERIODONTITIS

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БИОМАРКЕРЫ И ПРОГНОСТИЧЕСКИЙ ПОТЕНЦИАЛ РОТОВОЙ ЖИДКОСТИ ДЛЯ РАННЕЙ ДИАГНОСТИКИ ХРОНИЧЕСКОГО ПАРОДОНТИТА

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Currently, the diagnosis of chronic periodontitis in most countries involves the determination of several clinical parameters, some of which are subjective and may vary in accuracy. In addition, clinical parameters register only in the presence of significant damage to periodontal tissues, making it impossible to suspect the disease in its early stages. Therefore, searching for objective criteria for diagnosing chronic periodontitis is essential for the dentist. Clinicians can use Chairside diagnostic tests using whole saliva or gingival fluid for early diagnosis of chronic periodontitis. It is feasible to assess the risk of disease development, its progression and response to therapy by identifying biomarkers with high sensitivity and specificity. The review discusses five promising biomarkers that have shown the most favorable results. It provides comparative indicators of their sensitivity and specificity and the possibility of isolated application for the early diagnosis of periodontitis.

Keywords: chronic periodontitis, inflammatory mediators, biomarkers

В настоящее время в большинстве стран диагностика хронического пародонтита включает определение ряда клинических параметров, некоторые из которых являются субъективными и могут отличаться по точности. Кроме того, клинические параметры не могут определить текущее состояние заболевания, так как должно произойти значительное повреждение тканей пародонта, прежде чем эти диагностические параметры смогут подтвердить развитие заболевания. В связи с этим поиск объективных критериев диагностики хронического пародонтита имеет важное значение для врача стоматолога. Диагностические тесты в стоматологическом кресле с использованием цельной слюны или десневой жидкости могут применяться клиницистами для очень ранней диагностики хронического пародонтита, оценки риска развития, прогрессирования и ответа на терапию путем выявления биомаркеров, достоверность результатов которых связана с чувствительностью и специфичностью. В обзоре рассматриваются пять перспективных биомаркеров, которые показали наиболее многообещающие результаты, приведены сравнительные показатели их чувствительности и специфичности и возможность изолированного применения для ранней диагностики пародонтита.

Ключевые слова: хронический пародонтит, медиаторы воспаления, биомаркер

For citation: Zub A. A., Gaivoronskaya T. V., Sirak E. S., Grigoryan V. A., Laypanova F. M., Shchetinina E. E., Remizov N. O., Sirak A. G. BIOMARKERS AND PROGNOSTIC POTENTIAL OF ORAL FLUID FOR EARLY DIAGNOSIS OF CHRONIC PERIODONTITIS. *Medical News of North Caucasus.* 2022;17(2):217-221. DOI – https://doi.org/10.14300/mnnc.2022.17054

Для цитирования: Зуб А. А., Гайворонская Т. В., Сирак Е. С., Григорян В. А., Лайпанова Ф. М., Щетинина Е. Е., Ремизов Н. О., Сирак А. Г. БИОМАРКЕРЫ И ПРОГНОСТИЧЕСКИЙ ПОТЕНЦИАЛ РОТОВОЙ ЖИДКОСТИ ДЛЯ РАННЕЙ ДИАГНОСТИКИ ХРОНИЧЕСКОГО ПАРОДОНТИТА. *Медицинский вестник Северного Кавказа.* 2022;17(2):217-221. DOI – https://doi.org/10.14300/mnnc.2022.17054

Hb – hemoglobin
Il – interleukin
LPS – lipopolysaccharide
MIP – macrophage inflammatory protein
MMP – metalloproteinase
OPG – osteoprotegerin
PGE2 – prostaglandin E2
RANK – receptor activator of NF-Kappa-B
RANKL – receptor activator of nuclear factor kappa-B-ligand
SRP – scaling and root planning

Periodontitis is one of the most common diseases known to mankind. Epidemiological studies have confirmed that chronic periodontitis is between 35 and 50 percent in the adult population, with about 10 percent suffering from severe tooth loss [1]. In addition, it has recently been shown that severe chronic periodontitis is the sixth most common disease worldwide [2, 3].

The first problem of the periodontist in treating periodontal diseases is a timely and accurate diagnosis since the loss of connective detached attachment and bone tissue is a gradual and largely irreversible process [4]. At present, the following clinical parameters are «gold standard» diagnostics: gum bleeding and periodontal pocket depth during probing, clinical attachment loss and X-ray estimation of alveolar bone loss, which are used by clinicians to detect periodontal diseases and to measure the severity of the disease [5]. However, some of the above criteria are subjective and may differ in accuracy. No less important is the fact that these clinical parameters display information about the previous destruction of periodontal tissues and are not able to illustrate the future condition of tissues and identify persons in the «risk group» for the development of periodontal diseases [6]. This is due to chronic parodontitis, which progresses episodically, with alternating periods of aggravation and remission [4].

According to recent studies, scientists are seeking a diagnostic biomarker that can become a more reliable, simple, non-invasive tool and complement or, in some cases, replace the usual clinical parameters for diagnosing chronic periodontitis [7, 8]. The use of biomarkers in preventive and predictive medicine is currently fundamental. It is aimed at the early detection of risk factors and the presence or progression of the disease. They can also be used in personalized medicine, which is aimed at determining individual treatment methods for individual patients [9].

The diagnostic reliability of any biomarker depends on its sensitivity and specificity. Sensitivity is the ability of a biomarker to detect disease in patients who have the disease (i.e., a true positive result), and specificity is the ability of a biomarker to exclude illness in patients where the disease is absent (i.e., a true negative result) [10].

Oral fluid as a diagnostic tool.

Saliva and gingival fluid may serve as biological media for detecting periodontal disease biomarkers, as these natural environments are particularly promising due to their easy collection.

Saliva has excellent potential as a diagnostic fluid and has an advantage over blood serum and other bodily fluids due to the non-invasive collection method, smaller specimen aliquot and low economic cost [11]. While the benefits of saliva are obvious, some disadvantages must be considered. The analyzed substances are present in the saliva in smaller quantities, which means that the analyses must be highly sensitive [12]. Saliva contains several proteases that potentially destroy protein biomarkers [13], and the presence of mucin and cell residues makes saliva a complex fluid for operation [12]. Additional interferences include diurnal fluctuations in saliva flow rate, presence of xerostomy, systemic diseases or physiological conditions, and taking certain medications that may affect or limit saliva collection [11].

The gingival fluid consists of a blood serum transudate and components formed and secreted locally into the gingival slit in response to the action of bacterial biofilm [8, 14]. To date, more than 90 different components of saliva and gingiva have been proposed and evaluated for the diagnosis of chronic periodontitis. Numerous cytokines and chemokines, enzymes, and local tissue degradation products are released into the gum fluid during the development of inflammatory reactions in periodontal tissues. That is why the gum liquid is considered the most favorable environment for the identification of molecular biomarkers, which will be able to detect the current activity of the disease, predict the further progression of the disease and reflect the reaction to periodontal therapy [15]. The advantage is also a simple collection of gingival fluid, non-invasiveness and the possibility of simultaneous sampling from several parts of the oral cavity [8, 16].

Systematic reviews and meta-analyses have identified five promising oral fluid biomarkers as good candidates for early diagnosis of periodontitis [14, 17–19]:

Metalloproteinase-8 (MMP-8) is a collagenase of neutrophil cells and is one of the most studied and promising biomarkers of chronic periodontitis [20, 21]. Several studies have shown that elevated levels of MMP-8 are associated with chronic periodontitis and accelerated disease progression [22, 23]. In addition, recent reports have shown that local and system MMP-8 levels may reflect the degree of chronic periodontitis [21, 24]. Reliable differences in MMP-8 levels in saliva in periodontally healthy patients and patients with chronic periodontitis and gingivitis with a significant positive correlation of MMP-8 levels with all clinical parameters [6] have been demonstrated. It is essential that after SRP and conservative treatment of chronic periodontitis, MMP-8 values decrease significantly within 12 weeks [25].

However, there is significant heterogeneity in the MMP-8 diagnostic values reported by various studies: sensitivity varies from 55 % to 93 %, and specificity varies from 48 % to 99 % [6, 26] (Table). According to meta-analyses, in gingival fluid, sensitivity was 77 %, and specificity was 92 %. The saliva showed a decrease in the diagnostic reliability of MMP-8 as a biomarker: sensitivity – up to 72.5 %, and specificity – up to 70.5 % [17, 18].

Table

Diagnostic significance of determining the most promising biomarkers of chronic periodontitis in the oral fluid

Biomarker	Threshold value (Cut-off)	Sensitivity (Se), %	Specificity (Sp), %	Sources
Metalloproteinase-8 (MMP-8), ng/ml	37.0–383.9	75.0 (67.7–85.0)	65.0 (60.0–69.3)	[6, 20, 26, 35, 37, 38]
Interleukin-1β (IL-1β), pg/ml	24.0–446.0	79.0 (75.8–82.3)	83.0 (60.3–92.3)	[6, 35–38]
Interleukin-6 (IL-6), pg/ml	3.7–22.4	68.5 (57.5–80.5)	69.5 (57.0–83.5)	[6, 22, 35, 37]
Macrophage inflammation protein-1α (MIP-1α), pg/ml	1.12–3.28	95.0 (80.5–97.5)	93.0 (80.5–96.5)	[6, 50, 52]
Hemoglobin (Hb), mg/dl	0.5–1.25	75.0 (53.5–75.5)	75.0 (71.5–75.5)	[58, 59]

Over the past 15 years, there has been a significant increase in studies showing the association between MMP-8 and various periodontal diseases and its high predictive capacity. In clinical practice, there are kits for diagnosing chronic periodontitis and perioperative MMP-8 based, the sensitivity of which ranges from 83 % to 95 %, and the specificity of 96–98 % [22].

Interleukin-1β (Il-1β) is a pro-inflammatory cytokine involved in inflammation, immune regulation, and bone resorption in chronic periodontitis. Il-1β is mainly expressed by macrophages and dendritic cells in response to exposure to molecular patterns associated with pathogens or injury. Il-1β is secreted by gingival fibroblasts, periodontal cells, and osteoblasts [27]. After secretion, accumulated Il-1β triggers a series of inflammatory reactions and is involved in the pathogenesis of periodontitis. As a rule, Il-1β in the focus of inflammation is responsible for increased local blood flow, recruitment of leukocytes, and infiltration by neutrophilic cells [28]. In addition, Il-1β increases the expression of collagenolytic enzymes and matrix metalloproteinases (MMPs), which contribute to the degradation of the extracellular matrix and, in turn, lead to bone resorption and tissue destruction [27].

The influence of Il-1β on the ligand-receptor system RANK/RANKL/Osteoprotegerin (OPG) is another mechanism of bone resorption. In addition to directly increasing Il-1β levels of RANKL and thus stimulating osteoclastogenesis, Il-1β additionally increases prostaglandin E2 (PGE2) synthesis by fibroblasts [29], which also induces RANKL expression [27]. Il-1β also reduces the production of OPG, which is a soluble receptor for RANKL that prevents its binding to RANK [30]. Summarizing the above, we can conclude that Il-1β has a long-term and persistent effect on osteoclastogenesis, which leads to bone resorption [31].

Il-1β has been found at elevated concentrations in gingival fluid [25, 32] and saliva [25, 33] in chronic periodontitis in numerous studies. Clinical parameters were characterizing periodontitis, such as gingival index and probing depth, significantly correlated with the level of Il-1β in the gingival fluid [34]. According to the literature, the values of diagnostic reliability of Il-1β in saliva vary: sensitivity ranges from 54 % to 88 %, and specificity from 52 % to 100 % (Table).

Interleukin-6 (Il-6) is produced by macrophages, neutrophils, and endothelial cells in response to LPS of periodontopathogenic bacteria and plays both pro-inflammatory and anti-inflammatory roles. It is involved in inflammatory, regenerative, metabolic and nervous processes [39]. The pro-inflammatory effect of Il-6 is to activate the proliferation of antigen-specific B-lymphocytes and enhance the production of antibodies, as well as enhance the functional activity of osteoclasts and fibroblasts [40].

Numerous studies have shown that elevated levels of Il-6 have been found in gingival fluid [34, 41] and saliva [42, 43] in patients with chronic periodontitis. An increase in Il-6 was observed as the disease progressed, i.e., from mild to severe chronic periodontitis [44]. In addition, several studies have documented a decrease in the level of Il-6 in the primordial fluid after non-surgical periodontal therapy [45, 46]. According to some studies, the sensitivity of Il-6 in saliva ranged from 52 % to 80 %, while the specificity ranged from 48 % to 87 % [6, 35, 37, 38].

Inflammatory macrophage protein-1α (MIP-1α) is a member of the cysteine-cysteine chemokine family, secreted by macrophages, neutrophils, basophils, dendritic cells, lymphocytes, and epithelial cells and mediate granulocyte migration and adhesion [47]. MIP-1α is the most abundantly expressed chemokine in periodontal tissues, and its expression is localized in the connective tissue adjacent to the pocket epithelium of inflamed gingival tissues [48]. It is an upstream signaling protein that stimulates monocytes and osteoclast progenitor cells to become active osteoclasts in RANK/RANKL in a dose-dependent manner [49].

Several studies have shown a significant increase in MIP-1α saliva concentration in chronic generalized periodontitis but not gingivitis [6, 50]. It is suggested that elevated MIP-1α levels may reveal the latent presence of subclinical inflammation in clinically healthy shallow periodontal regions in chronic generalized periodontitis (Depth of sensing and level of clinical attachment of 3 mm without bleeding in sensing) [51], as evidenced by the decrease in the level of this indicator after non-surgical periodontal therapy [52, 53]. In addition, MIP-1α showed the strongest correlation with all clinical parameters of periodontal diseases [6, 52].

Diagnostic reliability assessment of MIP-1α in saliva as a biomarker of periodontal diseases showed 90.3 % sensitivity and 85.7 % specificity in aggressive periodontitis [54]. In the gingival fluid, the sensitivity and specificity of MIP-1α-diagnosis were 93.33 % and 98.73 %, respectively [55]. On average, researchers agree on the importance of this marker for diagnosing various forms of periodontitis.

Hemoglobin (Hb) is a protein localized in erythrocytes that transports oxygen to tissues and carbon dioxide from tissues to the lungs. In 2005, Hanioka T. et al. [56] described the content of Hb in the gingival fluid of shallow periodontal pockets. They suggested that clinically invisible bleeding had already occurred previously in the gingival sulcus at the initial stage of inflammation, despite a negative test for bleeding on probing. Other studies have confirmed this hypothesis. The detection of Hb obtained due to microtrauma in the gingival sulcus can indicate the preclinical diagnosis of chronic periodontitis [57]. According to some studies, the sensitivity of Hb in saliva ranged from 32 % to 76 %, and the specificity from 68 % to 76 % [58, 59].

Conclusions. Finding a biomarker for the early diagnosis of chronic periodontitis is of great interest to the scientific community. Despite a large number of studies on this topic, there is significant heterogeneity in the diagnostic values of the most promising biomarkers. It can be assumed that heterogeneity can be explained by several differences between studies, such as the methods used to identify biomarkers, the accepted thresholds, the degree and severity of the disease, and the age and ethnicity of the participants. It is also important to note that chronic periodontitis is episodic. Therefore, the cross-sectional design of the research may reflect the different biological phases of the disease, resulting in differences in biomarker expression levels [48].

On the other hand, many studies of questionable quality have been conducted, especially with small sample sizes. Accordingly, given the quality and heterogeneity of research in this area, the results must be interpreted cautiously. However, further progress in this direction still requires a more thorough examination of thresholds through longitudinal and well-designed studies with large sample sizes.

The future offers promising opportunities for gingival fluid as a diagnostic tool that provides a non-invasive, efficient and easy-to-use approach to the analysis of biomarkers of chronic periodontitis and will allow predicting future tissue destruction and diagnosing early signs of disease. In addition, it can also help track the response to treatment and help develop new therapeutic approaches with modulating drugs, leading to more individualized, targeted therapy for periodontal diseases.

Disclosures: The authors declare no conflict of interest.

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