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ROLE OF BIOMARKERS AS A DIAGNOSTIC CRITERIA DURING PERIODONTAL AND PERI-IMPLANT PATHOLOGIES EVALUATION

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Summary : Biomarkers can be described as substances, which can help to assess the adequacy of ongoing biological or pathological processes, and assist to evaluate appropriate pharmacological response during complex treatment. Due to the high prevalence of periodontal and implant associated lesions this article is devoted to the study of specific biomarkers peculiar to these pathologies that can be verified in the biological material from oral cavity, such as biochemical (Cystatins, α-glucosidase, Acid phosphatase, Alkaline phosphatase, Aminopeptidase, Lactoferrin, Translactoferrin, IgM, MMP-13, MMP-8, MMP-9), genetic (Cathepsin C genemutation, Collagen gene mutation, IL-1 polymorphisms, IL-10 polymorphisms, Tumor necrosis factor) and microbial (*Aggregatibacter actinomycetemcomitans*,*Campylobacter rectus*, *Mycoplasmas*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Peptostreptococcus icros* etc.) biomarkers that are systematized in this article. Also, the role of biomarkers associated with the periodontal and peri-implant pathologies that was found in works of other researchers are described in discussion section of the article. The question of clinically-associated and reliable diagnostic biomarkers selection in terms of assessing peri-implant or periodontal pathologies remains open in dental science and practice. Relevant biological agents should provide not only confirmation of clinically diagnosed periodontitis or peri-implantitis, but also serve as criteria for evaluating quality of the iatrogenic interventions, and provides prognostic risk assessment pathology occurrence with the definition of related clinically significant diagnostic parameters.

Key words : peri-implantitis, periodontitis, biomarkers, diagnostic role.

Introduction. In spite of the progressions and achievement of dental implants, poor dental cleanliness, lingering concrete, smoking, and other danger variables can prompt peri-implant lesions, which have many similarities with periodontal lesions. The pervasiveness of peri-implantitis as of now ranges from 12% to 43%. It is evaluated that 80% of American grown-ups with dental implants having some type of this sickness. The expanded improvement of maladies prompts the need to build up a counter measure that can minimize the effect in patients even after implantation [1, 2]. Analogical situation is also actual for patients with periodontitis [3, 4]. Due to the high prevalence of these pathologies among different age groups, it is recommended the utilization of salivary biomarkers to improve analytic affect ability for peri-implantitis and periodontitis malady appraisal. This paper is devoted to the analysis of biomarkers associated with peri-implantitis and periodontitis lesions and their systematization for further practical use.

Objective: to evaluate the role of biomarkers in the initial verification, progress identification and evaluation of treatment results for peri-implant lesions and periodontitis.

Material and Methods. Analysis of different clinical and experimental studies was provided via Google Scholar and PubMed systems. Obtained integrated data from 78 articles was presented in a form of review of the most relevant and significant results. Systematic approach was obtained by

the analysis of different types of biomarkers in different control and experimental groups with different stages of pathology and different clinical manifestations.

Results and Discussions. Biomarkers can be described as substances, which can help to assess the adequacy of ongoing biological or pathological processes, and assist to evaluate appropriate pharmacological response during complex treatment [5, 6, 7]. Propels in oral and periodontal infection analytic exploration are moving toward strategies whereby periodontal danger can be distinguished and evaluated by target measures, for example, biomarkers [6, 7, 8].

Gingival crevicular fluid (GCF), has increased extraordinary enthusiasm on conceivable indicative worth in periodontal ailment. It contains a substantial number of proteins and peptides got from aggravated host tissues [9]. The study of the GCF parts can reflect the infection status of individual destinations and in this way recognize potential biomarkers of periodontitis. A few delicate and solid markers are available in gingival crevicular to identify the vicinity, seriousness, and reaction to treatment [10]. The adjustments in the GCF constituents could be utilized as a potential marker as a part of the periodontitis movement. Chemicals, particularly proteinases, have a focal impact in the control of periodontal tissue turnover in well being and tissue pulverization in periodontitis. A portion of the chemicals incorporated into GCF incorporate Aspartate aminotransferase (AST), which is a solvent protein discharged to the extracellular environment upon cell passing. Another part is basic phosphatase; a film bound glycoprotein created by numerous cells such as leukocytes, osteoblasts, macrophages, and fibroblasts. Beta-glucuronidase (BG) is additionally one of the proteins included in the pulverization of noncollagenous parts of the extracellular grid and is considered as a pointer or indicator of periodontal illness action. BG adds to noncollagenous network debasement in periodontal malady, and its movement may be a decent pointer or indicator of periodontal sickness. Elastase is a protein discharged from polymorphonuclears (PMNs) to the gingival hole because of host-microbial connections. It is considered as a danger component for the improvement of periodontitis. Increased levels of GCF elastase chemical have been accounted for periodontitis. Cathepsin B is cysteine proteinases chemical and in GCF, it begins particularly from macrophages. The level of cathepsin B in the GCF is hoisted in patients with periodontitis. It has demonstrated an immediate connection to the seriousness of periodontitis. It additionally contains framework metalloproteinases (MMPs) are a group of chemicals in charge of the corruption of extracellular lattice segments, for example, collagen, proteoglycans, laminin, elastin, and fibronectin. They assume a focal part of the periodontal ligament (PDL) is renovating, both in physiological and obsessive conditions. MMP-8, in conjunction with MMP-9 and useful granulocyte elastase, is included in tissue demolition in subjects with periodontal illness [6, 7, 11, 12]. The bacterial plaque instigates the beginning to penetrate of incendiary cells in the gingival fissure including macrophages and lymphocytes [13] (Table 1) [13].

Table 1

Diagnostic tools to measure periodontal disease at the molecular, cellular, tissue, and clinical levels

Level	**Examples of Process**	**Example of Diagnostic Tools**
Molecular	Activation of receptors for endotoxin: CD-14; Toll-like receptors	CD-14; Toll-like receptors Polymerase chain reaction; NADNA hybridization; laser-capture microdissection
Cellular	Inflammatory cell activation such as neutrophils; osteoclast activation	ELISA;immunohistochemistry
Tissue	Downgrowth of junctional epithelium; bone and connective tissue loss	Histomorphometry; immunohistochemistry
Clinical	Attachment loss	Periodontal probing
	Bone loss	Radiographs

On the other hand, late advances in the utilization of biomarker-based diagnostics for illness action incorporate mediators that are discharged into GCF and spit can be comprehensively assembled by sources. Another source is host determined which constitutes 1L-β, Aspartate, Aminotransferase, Transferase, Grid proteins, Lactoferrin, and Lysozyme. The other source is from connective tissue breakdown items, which constitutes of Collagen-telopeptides, Osteocalcin, Proteoglycans, breakdown items, and Fibronectin parts. The last source are the incendiary middle people, which have supplement, cytokines, interleukins, Tumor rot component α, Interferon-α, antibacterial antibodies IgG, IgM, IgA, substance P, Prostaglandin E2, intense stage proteins, transferrin, and C reactive protein. Biomarkers are particular for periodontal ailment, which are thought to be the mirror of the source where they are created (Table 2) [14, 15]. The similar situation is relevant for the biomarkers of peri-implantitis lesions. Hultin et al. (2002) managed to diagnose some difference in enzymatic activity within peri-implantitis lesions: increased level of elastase activity and increased concentration of lactoferrin [16]. Ling Xu et al (2009) in turn revealed that the level of collagenase-2, as well as the extent of its activity, is significantly higher in samples collected from peri-implant sulcus fluid around the inflammatory compromised implants, compared with similar samples collected from sulcus around the teeth with the symptoms of gingivitis and chronic periodontitis [17]. Also in areas of peri-implantitis and chronic periodontitis were registered increased activity levels of matrix metalloproteinases and their isoforms. Such findings registered in higher parameters not only in respect to areas around healthy teeth, but relatively to the peri-implant locations without any signs of inflammatory lesion. As a result, scientists were able to conclude that peri-implantitis characterized not only by the individual characteristics of immune response, but also by topographically specific indicators. Bullon et al. (2004) also managed to identify elevated levels of T-cells in a sample study of aggressive periodontitis and peri-implantitis, while the level of vascular proliferation measured by histochemical reactivity was higher in patients with the compromised implants than in patients with impaired periodontal status or with healthy

periodontal tissues [18]. Similar results were obtained by the Recker (2015), who determined that the level of IL-17A and TNF-α is higher in sulcular fluid collected from patients with peri-implantitis, compared to healthy patients.

Table 2
Different types of biomarkers

Proteomic Biomarkers	**Genetic Biomarkers**	**Microbial Biomarkers**	**Other Biomarkers**
Cystatins, α-glucosidase, Acid phosphatase, Alkaline phosphatase, Aminopeptidase, Lactoferrin, Translactoferrin, IgM, MMP-13, MMP-8, MMP-9, Cathepsin B, Osteonectin, Osteocalcin, Osteopontin, Osteopontin, Elastase Platelet-activating factor, Epidermal growth factor, Platelet-derived growth factor, Esterase, Pyridinoline crosslinked carboxyterminal telopeptide, Fibronectin,sIgA(secretory IgA) Gelatinase, IgA, Trypsin, Vascular endothelial growth factor, IgG	Cathepsin C gene mutation, Collagen gene mutation, IL-1 polymorphisms, IL-10 polymorphisms, Tumor necrosis factor, Polymorphisms.	Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Mycoplasmas, Porphyromonas Gingivalis, Prevotella intermedia, Peptostreptococcus micros, Prevotella nigrescens, Treponema denticola, Tannerella forsythia. Treponema socranskii.	Calcium, Cortisol, Hydrogen sulphide, Methylmercaptan, Pyridine.

However, scientists have noted that the important role was played by the specificity of the test material, so the level of cytokines found in sulcular peri-implant fluid was significantly higher than those found in fluid of gingival sulcus. Casado et al. (2015) in turn proved the importance of the association of gene BRINP3 during peri-implantitis dynamics, regardless to its isolated nature or additional presence of periodontal lesions around the patient's natural teeth [19]. The analysis conducted by Zani et al. (2016) managed to identify the existing relationship between the presence of relevant biological markers in a peri-implant fluid and presence of possible pathology: 12 of the 20 studied biomarkers showed increased concentration during peri-implantitis (sCD40L, FGF-2, MDC, PDGF-BB, Eotaxin, MCP-3, Flt-3L, IL-13, IL-1β, IL-2, IL-6, TNFα, IL-10, IL-12, IL-17 and IL-15) [20]. Sánchez-Siles et al. (2015) after analyzing biomarkers of oxidative stress found that levels of myeloperoxidase in patients with peri-implant lesion was slightly higher than that of healthy patients, but this difference was not statistically significant [21]. Malik (2015) obtained similar results -

the average myeloperoxidase level were higher in the group of patients with the peri-implantitis, but again this difference was not statistically significant compared to the control group [22]. A retrospective study of Ramseier and Buser (2015) showed that the increase of MMP-8 and IL-1β in PISF or GCF may be associated with inflammatory lesions around the teeth or implants, in turn, a change in the ratio MMP-1 / TIMP -1 towards the decrease is a criteria of progression of the peri-implant pathology [23]. Sorsa et al. (2016) even recommend the use of MMP-8 with IL-1β concentration parameters not only as a diagnostic indicator, but also to calculate the cumulative risk of disease occurrence, and assessing the effectiveness of the treatment [24]. Rocha et al. (2014) were able to show that the level of IL-1β in patients with peri-implantitis is higher than in healthy patients, but the indicator's parameters was equal among patients with complete and partial adentia with the signs of peri-implant lesions [25]. Rakic et al.(2015) in the analysis of the three studied groups (patients with peri-implantitis, patients with peri-mucositis, and patients without peri-implant lesions), found that the presence of clinical peri-mucositis symptoms significantly increases the level of receptor activator of nuclear factor-κB and cathepsin-K, while the peri-implantitis further provoke increased levels of sclerostin. In a studied group of patients with the peri-implant pathology was found that the recent concentration of receptor activator of nuclear factor-κB (RANK), soluble RANK ligand (sRANKL), osteoprotegerin (OPG), cathepsin-K, and sclerostin is higher in comparison of healthy sample group [26]. Renvert S. (2015) in turn proved not only connection between increased levels of IL-1β, IL-8, TNF-α and VEGF in patients with peri-implantitis, but also the fact that the higher value of IL-1β were recorded among researched material with *E. coli* or *S. epidermidis* presence in it [27].

Conclusions. Thus in dental science and practice problem of optimal clinically-associated and reliable diagnostic biomarkers in terms of assessing criteria of peri-implant or periodontal pathology remains open. In the author's opinion relevant biological agents should provide not only confirmation of clinically diagnosed periodontal or peri-implant lesions, but also serve as a parameter for evaluating quality of the iatrogenic interventions and prognostic assessment for risk of disease occurrence in conjunction with the definition of related clinical aspects of diagnosis. Also, author found important the fact that the verification of appropriate biomarkers should be optimized to the diagnostic capabilities of laboratories with the possible development of further rapid methods of its identification to become a simple approach for the assessment of different pathologies parameters and to be affordable for implementing in a wide dental practice. The analysis of important agents, such as proteomic (Cystatins, α-glucosidase, Acid phosphatase, Alkaline phosphatase, Aminopeptidase, Lactoferrin, Translactoferrin, IgM, MMP-13, MMP-8, MMP-9), genetic (Cathepsin C gene mutation, Collagen gene mutation, IL-1 polymorphisms, IL-10 polymorphisms, Tumor necrosis factor) and microbial (*Aggregatibacteractinomycetemcomitans,Campylobacter rectus, Mycoplasmas, Porphyromonas Gingivalis, Prevotella intermedia, Peptostreptococcus micros* etc.) markers should be further developed for evaluation their precise role at that different pathologies stages.

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