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PERSONALIZED ORAL MEDICINE: INDIVIDUALIZED TREATMENT FOR PERIODONTAL PATIENTS

Narrative Review

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FACULDADE DE MEDICINA DENTÁRIA
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Personalized Oral Medicine: Individualized treatment for periodontal patients

A Narrative Review

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“Não é o trabalho, mas o saber trabalhar, que é o segredo do êxito no trabalho. Saber trabalhar quer dizer: não fazer um esforço inútil, persistir no esforço até ao fim, e saber reconstruir uma orientação quando se verificou que ela era, ou se tornou, errada.”

Fernando Pessoa,

em Teoria e Prática do Comércio: preceitos práticos

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INDEX OF ABBREVIATIONS

BOP	Bleeding on Probing
CRP	C-reactive protein
FDA	Food and Drug Association
GCF	Gingival Crevicular Fluid
HOMIM	Human Oral Microbe Identification Arrays
IL-1	Interleukin-1
IL-6	Interleukin-1 beta
OPG	Osteoprotegerin
NGS	Next-Generation Sequencing
PGE2	Prostaglandin E2
RANK	Receptor Activator of Nuclear Factor Kappa-B
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
SNP	Single Nucleotide Polymorphism
WHO	World Health Organization

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RESUMO

INTRODUÇÃO: A doença periodontal tem uma distribuição a nível mundial e pode definir-se como sendo uma patologia complexa e multifatorial, tratando-se de uma condição inflamatória crónica que afeta os dentes, o osso alveolar e o ligamento periodontal. Atualmente, persiste ainda um grande nível de incerteza no que diz respeito à previsão dos efeitos dos tratamentos existentes e na estabilidade dos mesmos. Perceber a etiologia desta patologia e identificar os fatores de risco envolvidos é essencial para estabelecer terapias periodontais eficazes e indispensável para que seja possível aperfeiçoar as medidas preventivas já existentes.

OBJETIVOS: O principal objectivo desta revisão narrativa é avaliar a aplicabilidade da medicina personalizada à área da medicina dentária, nomeadamente no âmbito da periodontologia, tentando desvendar de que formas pode ser alcançada e como pode ser levada aos pacientes periodontais.

MATERIAIS E MÉTODOS: Para a pesquisa de estudos científicos e revisões bibliográficas foram usadas as seguintes bases de dados: Pubmed (MEDLINE), Wiley (John Wiley & Sons), Scopus (Elsevier) e Science Direct (Elsevier). A pesquisa bibliográfica foi realizada no seguinte período: de 28/11/2021 a 15/04/2022, seguindo uma pesquisa em cadeia, sem nenhum critério de exclusão temporal.

DESENVOLVIMENTO: Ainda que a presença de placa bacteriana seja essencial para o desenvolvimento da doença periodontal, nem sempre a quantidade, nem mesmo as espécies bacterianas envolvidas, se correlacionam com a gravidade da doença em si. Os avanços feitos no âmbito dos testes genéticos, como é o caso do Next Generation Sequencing, podem permitir um sequenciamento mais rápido de um gene ou de um cromossoma inteiro, podendo ser utilizados clinicamente para diversos fins de diagnóstico. O fluído crevicular gengival tem sido alvo de estudos recentes, onde se identificou a presença de proteínas específicas, nomeadamente enzimas presentes no tecido periodontal inflamado. A saliva também foi identificada como sendo um fluido oral com elevada capacidade de diagnóstico. Os biomarcadores salivares, nomeadamente a Interleucina-1 e a Interleucina-6, podem ser considerados citocinas com elevado potencial prognóstico e preditivo.

CONCLUSÃO: A nossa abordagem em relação à periodontite se não deve limitar ao tratamento da doença em si, nem passar apenas pela eliminação dos sintomas. Devemos entender os princípios biológicos que influenciam a progressão da doença periodontal, para que seja possível preveni-la com eficácia e, consequentemente, orientar melhor nossos pacientes. O tratamento periodontal individualizado é o futuro da medicina dentária e esperamos que este possa ser integrado na prática clínica diária o quanto antes.

PALAVRAS-CHAVE: Medicina Oral Personalizada, Medicina Personalizada, Cuidado Oral Personalizado, Medicina Dentária Personalizada, Periodontologia Personalizada, Biomarcadores em Periodontologia.

ABSTRACT

INTRODUCTION: Periodontal diseases have a global distribution and are complex and multifactorial chronic inflammatory infections that affect the teeth, bone and soft support tissue. There can be a level of uncertainty in predicting successful periodontal site-specific treatment outcomes and stability. A correct understanding of the etiology of such a condition and identifying its risk factors is indispensable to establish effective periodontal therapies and crucial to refining disease-preventive measures and prognosis.

AIM: The aim of this narrative review is to evaluate the applicability of personalized medicine in dentistry, namely in the field of periodontology, unveiling the possible ways in which it can be achieved and how it can be delivered to periodontal patients.

MATERIALS AND METHODS: For the research of scientific studies and reviews, were used the following databases: Pubmed (MEDLINE), Wiley (John Wiley & Sons), Scopus (Elsevier) and Science Direct (Elsevier). The research was made between 28/11/2021 and 15/04/2022, following a hand searching with no time criteria of exclusion.

DEVELOPMENT: Even though it is crucial for periodontal disease initiation, the amount of plaque itself or even the bacterial species do not always correlate with disease severity. Advances in genetic testing, such as Next Generation Sequencing, can enable fast, vast, and deep sequencing of a portion of a gene or an entire genome and may be used clinically for a variety of diagnostic purposes. Recent investigations focusing on gingival crevicular fluid have identified the presence of specific proteins, particularly the enzymes released from inflamed periodontal tissue. Saliva has also been identified as being a host-derived oral fluid with potential diagnostic capabilities. Salivary biomarkers, namely Interleukin-1 and Interleukin-6 can be seen as possible prognostic and predictive factors.

CONCLUSION: Our approach to periodontitis should no longer be limited to treating the disease itself or eliminating symptoms. We must understand the biological principles that influence periodontal disease's progression, so we can efficiently prevent it and consequently better guide our patients. Personalized periodontal therapy is indeed the upcoming concept of dental treatment, and our future perspectives are that it can be integrated into daily dental practice as soon as possible.

KEY-WORDS: Personalized Oral Medicine, Personalized Medicine, Personalized Oral Care, Personalized Dentistry, Personalized Periodontology, Biomarkers in Periodontology.

INTRODUCTION

The concept of “Personalized Medicine” has suffered from great hype during the last decade and has been debated exhaustively in the scientific community (2,3).

Personalized medicine is a wing of medicine that offers the individualization of healthcare in which all decisions and treatments are tailored according to individual patient’s needs. Personalized medicine essentially leans on genetic information, proteomic information, and on the individual’s characteristics, in order to individualize the treatment. In addition to presenting itself as a new opportunity to providing better care and assistance to patients in general, it also presents itself as a unique and interesting challenge from a scientific point of view (2, 3).

Since each patient is unique and has different characteristics, personalized medicine is based on that same belief. As individuals possess nuanced and unique characteristics at the molecular, physiological, environmental exposure and behavioral levels, it is valid to think that they may need to have interventions provided to them that are tailored to these same characteristics (2, 3).

More and more, there is a growing need for a transition to more proactive and personalized medical care, with greater concern for disease prevention, early intervention and risk assessment, in order to minimize the onset and progression of chronic diseases (2, 3, 4).

With recent advances being made in genetics, proteomics, pharmacogenetics, and on the education of the patient population, there is the opportunity to deliver levels of personalized care more now than never before (2, 3, 4).

However, there is still no consensus on this topic. According to some authors, personalized medicine should be seen as a promising revolution. Others claim that this is still far from the predictive and preventive health paradigm, suggesting that it focuses more on speculation than on the obtained results (2, 3, 4).

Despite the fact that is a recent concept, it can also be applied to dentistry, in pathologies that have a high probability of becoming chronic. Although general dentists still might see individualized medicine as a concept of the future, the reality is that its application to everyday dentistry is closer than ever. The use of personalized medicine in the field of dentistry, namely in periodontology is progressing rapidly (2, 3, 4).

The oral cavity is one of the main gateways for pathogenic microorganisms, in addition to being a mirror that can reflect the patient's general state of health. For example, the role of inflammation appears to be the common denominator between periodontal disease and several systemic diseases. This emphasizes the importance of using salivary diagnostics, especially for monitoring periodontal diseases. For this implementation to be possible and successful, it is necessary to identify biomarkers, previously associated with specific diseases (4, 5, 9).

Periodontal diseases are multifactorial chronic inflammatory infections that affect both the bone and support soft tissue. Microorganisms present in the biofilm are the main etiologic factor that lead to the destruction of the supportive periodontal structures. Also, local and systemic factors play a significant role in the process of degradation and maintenance of the periodontium (9).

Periodontal disease itself is associated with a microbial component and a host defense component, with two genomes involved (that of the causative bacterium and that of the patient). Through genomic screening of bacterial plaque, more reliable information on the composition of oral biofilms can be obtained (5, 6).

Oral fluids, such as saliva or gingival crevicular fluid, have emerged as potential supplemental diagnostic tools and can be used for this purpose (9).

Periodontal tissue physiology and periodontal diseases are very complex and have provided challenges along the way toward reaching the goal of chair-side salivary diagnostics for individualized treatment and maintaining periodontal health (3, 6, 7).

Many studies have been published in the past decade that contribute to the notion that periodontal diseases may truly influence a number of systemic diseases, such as diabetes, cardiovascular events and osteoporosis (3, 6, 7).

In the case of this condition, some patients have a very noticeable immune response that actually forms an important part of the disease process. Also, understanding whether a patient has a low, normal or high inflammatory response through genetic testing, may allow for a better treatment option, where we not only focus on the pathogen itself, but we can also modulate the patient's response to that same agent (3, 6, 7).

Truth be told, great progress has already been made in human and microbial genomes, which allows not only a better understanding of the molecular basis of some diseases with oral manifestations, but also the creation of new diagnostics, therapies and biomaterials (4).

For this being, the reality is that its application in everyday dentistry is desirable, especially in the field of periodontology, which is what is going to be studied and explored in this narrative review (3, 8).

The main objective of this review is to demonstrate the applicability of personalized medicine to periodontology and to demonstrate in which that can be reached.

MATERIALS AND METHODS

For the research of scientific studies and reviews, were used the following databases: Pubmed (MEDLINE), Wiley (John Wiley & Sons), Scopus (Elsevier) and Science Direct (Elsevier)(1). Were also used a few web pages from health organizations.

The research was made between 28/11/2021 and 15/04/2022, using the following keywords: Personalized Oral Medicine, Personalized Medicine, Personalized Oral Care, Personalized Dentistry, Personalized Periodontology, Biomarkers in Periodontology.

As this is a particular recent subject of study, there are not many studies available about personalized medicine in the field of dentistry. Therefore, we had to follow a hand search with no time criteria of exclusion, in order to obtain the most information about the topic. We selected articles written in English, Spanish and Portuguese.

We started to look for using the keywords above and started from there. We analyzed all abstracts of the articles that addressed personalized medicine or personalized oral medicine and selected the ones focused on its mechanism and benefits/risks.

The general research was complemented by manual research by analyzing the bibliography of the selected articles, in a sequential way. We tried to relate the two concepts (periodontology and personalized medicine), towards gathering more concrete information.

DEVELOPMENT

PERSONALIZED MEDICINE: DEFINITION AND CURRENT APPLICATIONS

Personalized medicine can be sometimes called individualized, precision or even P4 medicine. The National Institutes of Health of the United States of America defines personalized medicine as “the use of an ‘individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease” but there are many other definitions to it. The Food and Drug Administration (FDA) defends that “personalized medicine can be envisioned as tailored therapy based on the interactions among genetic, clinical, and environmental factors affecting an individual” (12, 13).

Briefly, it is an evolving field in medicine in which are used diagnostic tests to determine which medical treatments are more appropriate for each person or even perform medical interventions to alter important molecular mechanisms that will have a direct impact on a patient’s health. This can be reached by combining data from those diagnostic tests with a person’s medical history, genetic information, environmental factors, and surrounding circumstances (13, 16).

The term “P4 medicine” was conceived by Dr. Leroy Hood and has been publicized as the "future of medicine”. It is a wellness model where the objective of patient management is to focus on the patient’s overall well-being rather than just treating the disease itself. This model consists of participation, prediction, prevention, and personalization (10, 15).

Participation stands for “to rely greatly on the positive contributions of activated patients and consumers” (15).

Prediction stands for the ability to predict the probable future emergence of disease-perturbed networks in patients (15).

Prevention stands for the ability to design preventive drugs that will avoid the development of these disease-perturbed networks and their cognate diseases (15).

Personalization stands for the ability to treat each patient as a unique individual and not as a statistical average (15).

One of the crucial factors in P4 medicine is recognizing that disease development and progression can be in part associated with a change in allostasis ("defined as the process of maintaining homeostasis through the adaptive change of the organism's internal environment to meet perceived and anticipated demands"). Several frequent chronic diseases, such as gingivitis and periodontitis, can be indeed a consequence of allostatic overload, which is defined as 'the price the body pays for containing the effects of arousing stimuli and the expectation of negative consequences". It involves the interaction of various physiological systems at different stages of activity. When environmental challenges are too extreme for the individual to be able to cope with, then allostatic overload ensues (15, 33).

By combining all these precision medicine concepts, it is possible to incorporate novel diagnostics, risk measurements, patient participation, and technological advancements to improve healthcare delivery (15).

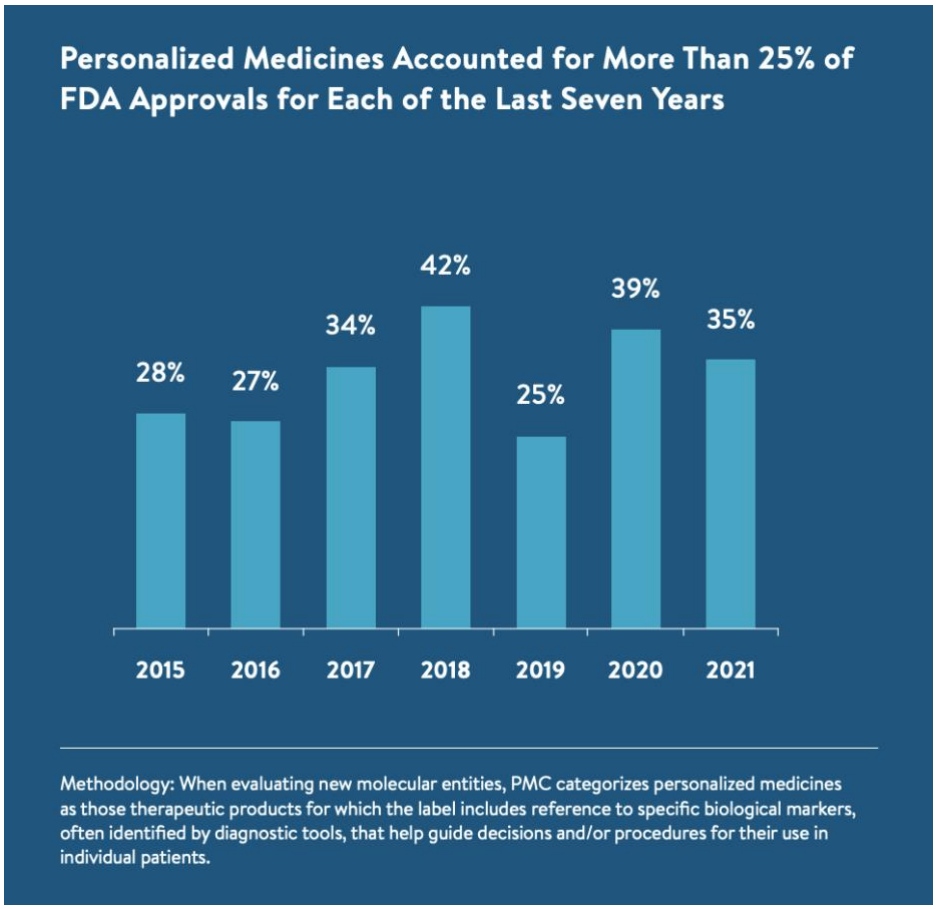
Advances in genetic testing, such as Next Generation Sequencing (NGS), can enable fast, vast, and deep sequencing of a portion of a gene or an entire genome and may be used clinically for a variety of diagnostic purposes (12).

The adoption of NGS-based tests in research and clinical practice is giving rise to the identification of a growing number of genetic variants. Being conscious of the clinical importance of these genetic variants holds high promise for the future of personalized medicine (12).

Even though it is a promising concept for patients and healthcare systems and there have been many revolutionizing and truly personalized innovations in the medicine area, this type of therapy is still not the first choice of most clinical practitioners (16).

In the past year of 2021, there have been approved new 17 personalized medicines, according to FDA (13).

This next figure represents the fast increase in the acceptance and adoption of personalized medicine. Just a decade ago, this concept accounted for less than 10 percent of the new therapies approved every year. Nowadays, these type of therapies represents more than a quarter of the new drugs the FDA has approved for the past seven years (13).



#13 Figure 1. Image taken from the FDA's website with the author's authorization, that shows personalized medicines approved by FDA from 2015 to 2021.

Clinical use of personalized medicine is particularly applied in oncology and rare disorders and has showed benefited patients. This is a relevant model. However, this might not translate well for chronic diseases. In chronic diseases, many of the bigger risk factors are environmental or acquired. For common chronic diseases just like periodontitis, the biology is not as deterministic as in oncology, and the clinical expression is a combination of multiple genes and environmental factors (10).

NECESSITY OF INDIVIDUALIZED PERIODONTAL TREATMENT

The oral cavity is one of the main gateways for pathogenic microorganisms, in addition to being a mirror that can reflect the patient's general state of health. For example, inflammation seems to be the common denominator between periodontal disease and other systemic diseases (4, 5, 9).

Periodontal diseases, such as gingivitis or periodontitis, have a global distribution and are complex and multifactorial chronic inflammatory infections that affect the teeth, bone and soft support tissue (9-13)

Periodontitis has been described as “episodes of acute exacerbations of destruction followed by periods of quiescence and stability” (Goodson et al. 1982, 1984, Socransky et al. 1984). A correct understanding of the etiology of periodontal diseases is indispensable to establish effective periodontal therapies. Local and systemic factors play a significant role in destroying and maintaining the periodontium (9-13).

Therefore, bacterial content is indeed the initiator. However, disease progression, intensity, and duration also depend on genetic and environmental parameters directly related to the host (9-13)

Identifying the risk factors and the direct causes of the disease itself is crucial to refining disease-preventive measures and prognosis. Some of these risk factors are modifiable, such as the oral-hygiene status of the host, infectious agents, tobacco smoking habits, diabetes mellitus control, and obesity. Others cannot or are unlikely to be altered. These include genetic predisposition to the disease, aging, socioeconomic status, and chronic psychosocial stress. (9 – 13, 19)

It has long been recognized that systemic diseases can directly influence the severity of periodontal disease. However, many studies have been published that defend that periodontal diseases may truly influence a plethora of systemic diseases, such as diabetes, cardiovascular pathologies, and osteoporosis. The observed associations can be due to direct infection, systemic inflammation, or molecular mimicry (9, 14).

There can be a level of uncertainty in predicting successful periodontal site-specific treatment outcomes and stability. Ongoing clinical assessments for periodontal disease severity determination are pocket depth, clinical attachment level, bleeding upon probing, gingival inflammation, plaque presence or level of oral-hygiene care, suppuration, and radiographic bone loss (9).

The primary goal of periodontal treatment is to reduce morbidity and repair function, so that life quality can be enhanced by objectively diagnosing a patient's periodontal health condition and well-being (26).

One of the biggest barriers to periodontal disease diagnosis is that the concrete diagnosis is only possible after the biological onset of the disease process. Not to mention that measurement errors, such as probing angulation and force, can and many times do interfere with proper measurements of attachment level (9).

Also, bleeding on probing (BOP) may occur in the absence of the disease (27).

This clinical method is indeed helpful for assessment but alone is unable to determine disease activity or future risk of structure loss and can even distort clinical treatment planning if it is not done meticulously. An ideal diagnostic tool should not only detect the presence and severity of the disease but also predict the subsequent course of the infection (9, 20, 26).

Along with this, it is known already that the single presence of pathogenic bacteria is not the cause of periodontal damage, in the majority of cases (9, 13). This can be seen in cases where periodontitis only affects a few teeth, despite an overall presence of "periodontopathic" bacteria in saliva. Also, many periodontitis lesions are self-limiting in time, despite the constant presence of pathogenic bacteria in the periodontal pocket (14).

For example, patients with a high content of microbial plaque and calculus might show almost zero bone loss, whereas patients with good clinical parameters may present severe bone loss. Then as well, drug therapy also has distinct clinical outcomes based on patients' genetic information and capacity to metabolize the drugs. Some individuals are poor metabolizers, whereas others metabolize drugs immediately (12).

Even though it is crucial for periodontal disease initiation, the amount of plaque itself or even the bacterial species do not always directly relate to disease severity. This takes place since the nature of the oral microbiome mostly depends on its interaction with the host. Host genetics do play a significant role in the establishment of the microbiota. Recent data showed that each individual has a particular dose-dependent response to bacteria that will determine their susceptibility to diseases, such as periodontitis. This emphasizes the importance and growing need to innovate the ways of diagnosis with the capability of detecting real-time changes in the periodontium. Such thing can be reached through the analysis of oral fluids, including gingival crevicular fluid and saliva (9).

However, for this implementation to be possible and successful, it is necessary to identify biomarkers, previously associated with specific diseases (9, 10).

RISK FACTORS IN PERIODONTITIS

In medicine, the risk is defined as the probability that a threat will cause some harmful event. Therefore, a risk factor is a characteristic that increases the probability of the event occurring (21).

At the individual level, the WHO defines risk factor as “any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury” (22).

In chronic diseases, the analysis of risk factors is critical to the decision-making process. The definition and evaluation of risk factors is of great importance in the understanding of the pathogenesis of periodontitis, as well as in its prevention and treatment (21, 23).

Periodontal risk combines both non-oral exposures and many oral characteristics that are essential to the decision-making process. Thus, risk factors can be divided into general risk factors (such as nutrition, diabetes or obesity), and local risk factors (such as an overhanging filling or root anatomy) (23).

A risk factor may or may not be changed. Non-modifiable risk factors include age, gender, genetics, and ethnicity. Modifiable risk factors include most local risk factors and systemic diseases. Besides being under the health professional’s control, these can also be under the control of the patient, such as oral hygiene or quitting smoking. Modifiable risk factors may also depend on the social environment (23).

Prior history of periodontitis is strongly associated with future risk. Various risk factors may be additive or conditional. The Periodontal Risk Assessment system, developed by Lang & Tonetti, is one of the tools that integrate multiple risk factors in the assessment of periodontitis (10).

This system allows the identification of individuals who may be predisposed to disease progression. The risk may or not involve interaction between risk factors, but the system acknowledges a vast range of risk factors without forcing the system to include all factors (10).

This involves a long and exhausting process that demands 3 successive steps: to identify potential risk factors, to clinically validate those considered to be risk factors, and to demonstrate the clinical utility of the use of specific risk factors (10).

A risk factor with a logical association and evidence to support causality is more prone to influence a particular clinical outcome. Identifying individual risk for periodontitis is important to help select patients who are more prone to develop moderate-to-severe generalized periodontitis; to exhibit clinical progression against typical periodontal therapy or to have periodontitis that has a direct influence on the development of systemic diseases (10, 14).

As with most chronic diseases, recent studies suggest that people with periodontitis follow a small number of clinical paths that translate into progression and severity patterns in the population (10).

The clinical validity relative to individual risk for periodontitis can be reached by demonstrating that risk stratification of individuals leads to different outcomes, disease progression, complications such as tooth loss, progression following treatment, and direct influence on other systemic diseases (10).

The aim of applying P4 medicine to periodontitis is to be able to identify patients who may benefit from using more intensive therapy during the primary stage of their treatment. This might include more intensive bacterial control (using systemic or local antimicrobials) and efforts to control risk factors themselves (15).

With risk factors control, we are talking about diabetes type 2 control, better nutritional approaches, or more direct control of inflammation by prescribing particular drugs (17).

In addition to this, the association between periodontitis and the progression of rheumatoid arthritis also appears to relate directly to the effects of oral bacteria (17).

However, when we are studying genetic factors in severe periodontitis, false positives may appear. This can happen when a specific genetic factor is present, but extractions have classified a patient as having mild periodontitis (17).

Not only does questioning disease progression and response to treatment allow us to get close to clinical utility, but also avoids various challenges inherent to case-control studies of periodontitis.

SALIVA AS A TOOL OF DIAGNOSIS IN PERIODONTOLOGY

As was previously mentioned in this review, it is well established that the presence of pathogenic bacteria alone does not induce periodontal damage in most cases. One hypothesis is that bacteria stimulate and release proinflammatory cytokines or acute-phase proteins that intensify or even initiate the disease process (9).

Some recent investigations focusing on gingival crevicular fluid (GCF) have identified the presence of specific proteins, particularly the enzymes released from inflamed periodontal tissue. GCF is a serum found in the gingival sulcus that carries biological molecular markers gathered from the surrounding surfaces. GCF is an attractive oral fluid considering it is easy to collect (20).

There have also been released some studies on the saliva being a host-derived oral fluid with potential diagnostic capabilities. Saliva is rich in albumin serum and in antimicrobial and immunomodulatory proteins, which contribute to the lubrication of mucosa and global maintenance of the integrity of the oral cavity. There might be potential to identify biomarkers in saliva for diagnosing periodontal diseases and monitoring their progression (9).

One of the advantages of using saliva as a ‘real-time’ diagnostic tool is the fact that it can be collected without any discomfort to the patient. Unlike a blood draw or a urine sample, saliva can be collected in a non-invasive way (9).

The study of salivary proteins provides a better interpretation of the complex cellular functional interactions. Consequently, the biologic biomarkers of health and disease can be better understood and grant better implementation of proper and personalized medical strategies (9).

There is the Saliva Proteome Knowledge Base that is available to the public and contains all the collected proteomic data and the identified salivary proteins.

. This database has become crucial in the identification of distinct combinations of biomarker panels that might provide different diagnostic information (9).

Salivary diagnostics shall become a reality in the near future if the development of analytical tools and reproducible biomarkers keeps evolving (9).

BIOMARKERS IN PERIODONTOLOGY

A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention”, according to the Biomarker Definition Working Group of 2001 (23).

Biomarkers can be seen as prognostic and predictive factors. Several salivary biomarkers have been studied to be able to predict the severity, progression, and frequency of periodontal diseases (23).

A cross-sectional study concluded that the combination of biomarkers found in saliva and periodontal pathogens indicated potential diagnostic value for identifying periodontal disease status (28).

The same patient population also demonstrated that salivary biomarkers and periodontal pathogens were able to predict periodontal disease progression (29).

Even though independent biomarkers have recently been subject of study as indicators of periodontal disease progression, it is unlikely that one alone is sensitive and specific enough to meet the criteria of a diagnostic tool. That is why there are groups of salivary biomarkers that may be promising for differential diagnosis, treatment planning, and identification of risk patients (9, 10, 18).

Periodontal destruction is managed by various mediators, including cytokines, which are soluble protein molecules that have the ability to transmit signals to other cells. These play a key role in initiating and pursuing immune and inflammatory responses since they stimulate the production of secondary mediators that will then call a cascade of events that amplify the inflammatory (9, 10).

Periodontal disease can be divided into three phases: inflammation, connective tissue degradation, and bone turnover. During each one, individual biomarkers have been identified (9).

In the initial stage of inflammation, there have been identified a plethora of cytokines, such as prostaglandin E2 (PGE2), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha. These are known to be released from cells such as junctional epithelial, connective tissue fibroblasts, macrophages, and polymorphonuclear neutrophils (9).

In the connective tissue degradation stage, there have been identified matrix metalloproteinase-8, matrix metalloproteinase-9, and matrix metalloproteinase-13, known to be powerful enzymes. They are released at the infected site, which leads to the degradation of connective tissue collagen and causes alveolar bone loss (9).

As bone turnover starts, IL-1 and RANKL levels are higher. Bone-specific biomarkers, essentially pyridinoline cross-linked carboxyterminal telopeptide of type I collagen appear in the surrounding tissue. They tend to go from the gingival crevicular fluid into the periodontal pocket and lastly into the saliva, becoming its component (9).

IL-1 is probably the proinflammatory cytokine that plays a key role in chronic inflammation. It is mostly produced by monocytes, polymorphonuclear neutrophils, fibroblasts, epithelial cells, endothelial cells, and osteoblasts. Interleukin-1 stimulates enzymes necessary to produce PGE2 and helps to control metalloproteinases and their inhibitors. This cytokine induces osteoclastogenesis, which leads to permanent alveolar bone loss. It is also strongly correlated with periodontal disease progression and studies have considered it to be a good biomarker for discriminating between active and inactive periodontal stages (9, 10).

One other important cytokine to the process of chronic inflammation is IL-6. Higher salivary levels of interleukin-6 have been related to the presence of gingivitis and are present in individuals with periodontitis (9, 10).

Some authors have identified that individuals with deep pocket depths and more severe BOP had elevated levels of GCF Interleukin-1b and Interleukin-6 (24, 25).

A recent study was made and concluded that all of the biomarkers except C-reactive protein (CRP) showed significant differences in the median levels of the stable and progressing patients. IL-1b had the highest significant difference ($p < 0.001$), indicating statistically significant higher levels of GCF IL-1b in the patients who had disease progression compared to the ones who did not (20).

The second GCF biomarker that demonstrated significance between the stable and progressing patient group medians was osteoprotegerin (OPG), showing a p-value of 0.003. OPG inhibits osteoclast differentiation and activity in a competitive way. OPG also acts like a “false target” to prevent RANK from connecting to RANKL (20, 32).

Since periodontal disease is a multifactorial disease, one must look beyond an individual biomarker and consider combinations of valuable host responses in order to provide the highest levels of sensitivity and specificity for disease progression (20).

Table 1. Biomarkers and their destructive role in periodontitis

TYPE OF BIOMARKER	BIOMARKER	FUNCTION / ROLE
Inflammatory	Interleukin-1 beta	Chronic inflammatory stimulator. strongly correlated with periodontal disease progression (I, II)
	Interleukin-6	Regulates immune and inflammatory responses. Related to the presence of gingivitis and periodontitis (I, II)
	C-reactive protein	High levels related to severe periodontal disease (III)
	RANKL	High levels when there is inflammation and periodontal degradation, in the presence of *Aggregatibacter actinomycetemcomitans* (I)
Alveolar bone turnover	Osteoprotegerin	Inhibits osteoclast differentiation and activity in a competitive way (III, IV)
	Interleukin-1 beta	Induces osteoclastogenesis, which leads to permanent alveolar bone loss (III)
	Prostaglandin E2	Found to increase osteoclast proliferation. Contributes significantly to bone loss related to periodontal disease (I, II)

I. Korte DL, Kinney J. (2016)
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PERSONALIZED MEDICINE IN PERIODONTOLOGY

Oral microbiota is composed mostly of bacteria and viruses that interact with each other and with the host. Recent studies have defended that interindividual and intraindividual variability in bacterial microbiota composition might be the cause for the occurrence of periodontal disease in one patient and not in others. Bacterial genome sequencing makes it possible to determine the composition of the oral microbiome (12).

Epigenetics has become an emerging field in periodontology when it comes to personalized medicine. Epigenetic factors have the potential to influence gene transcription and therefore contribute to disease risk, extent, and severity. Epigenetics is now working on ways to develop dynamic mechanisms that are able to predict environmental and behavioral factors that influence gene expression and consequently modify individual risk for periodontitis (18).

This makes it possible to analyze interaction effects for individuals with multiple diseases, such as diabetes type 2 (18).

Personalized periodontal medicine has also become important in pharmacogenomics. Pharmacogenomics is a domain that aims to describe how can human genetic variants influence drug-response phenotypes and that intends to identify what specific drugs and doses are most likely to be efficient and safe for each patient, with almost no side effects attached (12).

Variations of drug metabolism-related genes have an important effect on drug assimilation. Drug therapy also has distinct clinical outcomes based on patients' genetics and capacity to metabolize the drugs. That is why genotyping patients is beneficial to minimizing side effects (12).

Such advances allow epigenetic biomarkers and pharmacogenomics to be considered as potential diagnostic and therapeutic tools to influence periodontal disease status (12, 18).

There have been used high-throughput technologies including SNP genotyping, NextGen sequencing, Omics techniques, and HOMIM (human oral microbe identification arrays) to determine the genetic, protein, and bacterial profiling of the individual. These technologies can be used to search for polymorphisms previously associated with higher susceptibility to periodontal diseases (12).

Customized platforms for SNP genotyping allow patient genetic records to be compared to other diagnostic screening tests, looking for one or two SNPs (12).

For example, one can extract DNA from a biological sample and test it for SNP genotyping of many genes for proinflammatory cytokines, previously mentioned as being related to a higher risk of periodontal diseases. We can also look for SNPs of genes that influence the bone remodeling process (such as RANKL and OPG). Finally, proteomics technology can be used for early diagnosis and prevention of disease progression through the detection of protein signatures in periodontitis (12).

Another way of implementing a P4 medicine approach in periodontal therapy is by using systems biology. This technique uses computational methods, such as mathematical modeling and simulation technologies, which are often combined with high-dimensional datasets (15).

CONCLUSION

Physicians, doctors, and dentists have long used personalized approaches to treat their patients. However, it is important to understand the biology that goes behind the procedures so that one can predict the clinical outcome. Personalized medicine is generally composed of two elements: the drug or other therapeutic intervention, and the diagnostic test.

A better understanding of the protective and destructive immune reactions of the periodontium may give rise to new therapies against destructive periodontal disease. Patients' genetic profiles are essential to anticipate the performance of drug therapy and minimize its side effects. Ongoing metagenomic studies have already established there is interindividual and intraindividual variability in bacterial biofilm composition. By using this approach, we manage clinical assessment and subclinical profiles to develop actual individualized diagnosis, prognosis, and treatment algorithms.

Prior history of periodontitis is strongly associated with future risk and biomarkers can be seen as prognostic and predictive factors. Several salivary biomarkers (namely Interleukin-1, Interleukin-6 and C-reactive protein) have been studied and identified as being able to predict the severity, progression, and frequency of periodontal diseases.

Salivary diagnostics might become a reality in the near future with the fast development of analytical tools and reproducible biomarkers in periodontology. When considering this possibility, one can imagine its implementation at various levels, such as screening, disease detection, monitoring of treatment outcomes, and identification of refractory or progressing cases. However, since periodontal disease is a multifactorial condition, is mandatory to isolate its effects.

To conclude, our approach to periodontitis should no longer be limited to treating the disease itself or eliminating symptoms. We must understand the biological principles that influence periodontal disease's progression, so we can efficiently prevent it and consequently better guide our patients.

Personalized periodontal therapy is indeed the upcoming concept of dental treatment, and our future perspectives are that it can be integrated into daily dental practice as soon as possible.

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APPENDIX

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DECLARAÇÃO

Mestrado Integrado em Medicina Dentária
Monografia / Relatório de Estágio

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Identificação da Publicação

Dissertação de Mestrado Integrado (Monografia) ☒ Relatório de Estágio ☐

Título Completo

Personalized Oral Medicine: Individualized Treatment for Periodontal Patients

Orientador Luzia da Conceição Martins Mendes Gonçalves

Palavras - chave Personalized Oral Medicine, Personalized Medicine, Personalized Oral Care, Personalized Dentistry, Personalized Periodontology, Biomarkers in Periodontology

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DECLARAÇÃO

Monografia / Relatório de Estágio

Declaro que o presente trabalho, no âmbito da Monografia/Relatório de Estágio, integrado no MIMD, da FMDUP, é da minha autoria e todas as fontes foram devidamente referenciadas.

27 / 05 / 2022

Joana Martinho Rocha

(O/A Estudante)

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