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13.00.02 Ta'lim va tarbiya nazariyasi va metodikasi (sohalar bo'yicha)
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MUNDARIJA

PERSONALIZED APPROACH TO THE TREATMENT OF GENERALIZED PERIODONTITIS IN THE PREDICTION OF CARDIOVASCULAR COMPLICATIONS BASED ON SALIVARY PROTEOMIC PROFILING

Shodiev O. U.
Scientific advisers: DSc., Prof.

Nazarova N. Sh.
DSc., Prof.

Agababyan I. R.
Samarkand State Medical University, Samarkand, Republic of Uzbekistan

Abstract: One known modifiable risk factor for cardiovascular diseases (CVD) is chronic generalised periodontitis (CGP). One interesting avenue in personalised medicine is the use of oral fluid biomarkers for non-invasive monitoring of concomitant pathology.

Purpose of the research. To create and scientifically validate an algorithm for the early prediction of cardiovascular problems in patients with concurrent pathology based on proteomic profiling of the oral fluid, as well as a customised treatment for CGP.

Techniques. There were 140 participants in the research (65 patients with CGP and cardiovascular risk who got personalised treatment made up the main group; 45 patients with CGP on conventional therapy made up the comparative group; and 30 healthy persons made up the control group). A thorough biochemical, cardiological, and dental examination was carried out. ELISA and LC-MS/MS mass spectrometry were used to assess the proteome profile of saliva (apolipoproteins A1, B, E, and cytokines). LASSO regression and ROC analysis were used for statistical analysis in R and Python environments.

Outcomes. For the first time, the idea of the "salivary lipoprotein signature of periodontitis" (ApoB/ApoA1 ratio in saliva >1.3) was confirmed as an indicator of disturbance of systemic lipid homeostasis. Unfavourable outcomes were shown to be independently predicted by the ApoE-ε4 isoform. A prognostic model (AUC >0.90) was created and included in the "PerioCardio-Risk" program. In 75-85% of patients, the salivary profile returned to normal and the periodontal pocket depth was reduced by 25-35% thanks to personalised treatment.

In conclusion. It is possible to optimise CGP therapy and anticipate cardiovascular risks two to five years before they appear clinically by including salivary proteome profiling into an interdisciplinary strategy.

Key words: chronic generalised periodontitis, cardiovascular diseases, salivary proteomics, apolipoproteins, personalised treatment, proteomic profiling, cardiovascular risk prediction.

Annotatsiya: Yurak-qon tomir kasalliklari (YQTK) uchun ma'lum bo'lgan o'zgartirilishi mumkin bo'lgan xavf omillaridan biri surunkali generalizatsiyalashgan periodontit (SGP) hisoblanadi. Shaxsiylashtirilgan tibbiyotdagi istiqbolli yo'nalishlardan biri hamroh patologiyalarni noinvaziv monitoring qilish uchun og'iz suyuqligi biomarkerlaridan foydalanishdir.

Tadqiqot maqsadi. Og'iz suyuqligining proteomik profillanishiga asoslangan holda hamroh patologiyaga ega bemorlarda yurak-qon tomir asoratlarini erta bashorat qilish algoritmini yaratish va ilmiy asoslash, shuningdek, SGP uchun shaxsiylashtirilgan davolash usulini ishlab chiqish.

Tadqiqot usullari. Tadqiqotda 140 nafar ishtirokchi qatnashdi (65 nafar SGP va yurak-qon tomir xavfiga ega bo'lib, shaxsiylashtirilgan davolash olgan bemor asosiy guruhni; 45 nafar SGP bilan an'anaviy davolash olgan bemor taqqoslash guruhini; 30 nafar sog'lom shaxs nazorat guruhini tashkil etdi). Keng qamrovli biokimyoviy, kardiologik va stomatologik tekshiruvlar o'tkazildi. So'lak proteomi profili (apolipoproteinlar A1, B, E va sitokinlar) ELISA hamda LC-MS/MS massa-spektrometriyasi yordamida baholandi. Statistik tahlil R va Python muhitlarida LASSO regressiyasi hamda ROC tahlili yordamida amalga oshirildi.

Tadqiqot natijalari. Birinchi marta "periodontitning so'lak lipoprotein signaturasi" (so'lakdagi ApoB/ApoA1 nisbati >1,3) tizimli lipid gomeostazi buzilishining ko'rsatkichi sifatida tasdiqlandi. ApoE-ε4 izoformasi noqulay natijalarni mustaqil ravishda bashorat qiluvchi omil ekanligi ko'rsatildi. Prognostik model (AUC >0,90) yaratildi va "PerioCardio-Risk" dasturiga kiritildi. Shaxsiylashtirilgan davolash natijasida bemorlarning 75-85 % ida so'lak profili me'yoriga qaytdi va periodontal cho'ntak chuqurligi 25-35 % ga kamaydi.

Xulosa. So'lak proteomini profillashni fanlararo yondashuvga kiritish orqali SGPni davolashni optimallashtirish hamda yurak-qon tomir xavflarini ular klinik jihatdan namoyon bo'lishidan ikki-besh yil oldin bashorat qilish mumkin.

Kalit so'zlar: surunkali generalizatsiyalashgan periodontit, yurak-qon tomir kasalliklari, so'lak proteomikasi, apolipoproteinlar, shaxsiylashtirilgan davolash, proteomik profillash, yurak-qon tomir xavfini bashorat qilish.

Аннотация: Одним из известных модифицируемых факторов риска сердечно-сосудистых заболеваний (ССЗ) является хронический генерализованный пародонтит (ХГП). Одним из перспективных направлений персонализированной медицины является использование биомаркеров ротовой жидкости для неинвазивного мониторинга сопутствующей патологии.

Цель исследования. Создать и научно обосновать алгоритм раннего прогнозирования сердечно-сосудистых осложнений у пациентов с сопутствующей патологией на основе протеомного профилирования ротовой жидкости, а также разработать персонализированный подход к лечению ХГП.

Методы исследования. В исследовании приняли участие 140 человек (65 пациентов с ХГП и сердечно-сосудистым риском, получавших персонализированное лечение, составили основную группу; 45 пациентов с ХГП, получавших традиционную терапию, составили группу сравнения; 30 здоровых лиц вошли в контрольную группу). Проведено комплексное биохимическое, кардиологическое и стоматологическое обследование. Профиль протеома слюны (аполипопротеины A1, B, E и цитокины) оценивали с использованием ELISA и масс-спектрометрии LC-MS/MS. Статистический анализ выполнялся в средах R и Python с применением LASSO-регрессии и ROC-анализа.

Результаты исследования. Впервые подтверждена концепция "слюнной липопротеиновой сигнатуры пародонтита" (соотношение ApoB/ApoA1 в слюне >1,3) как индикатора нарушения системного липидного гомеостаза. Показано, что изоформа ApoE-ε4 является независимым предиктором неблагоприятных исходов. Создана прогностическая модель (AUC >0,90), включённая в программу "PerioCardio-Risk". Благодаря персонализированному лечению у 75-85 % пациентов профиль слюны нормализовался, а глубина пародонтальных карманов уменьшилась на 25-35 %.

Заключение. Включение протеомного профилирования слюны в междисциплинарную стратегию позволяет оптимизировать лечение ХГП и прогнозировать сердечно-сосудистые риски за два–пять лет до их клинического проявления.

Ключевые слова: хронический генерализованный пародонтит, сердечно-сосудистые заболевания, протеомика слюны, аполипопротеины, персонализированное лечение, протеомное профилирование, прогнозирование сердечно-сосудистого риска.

INTRODUCTION

Within the context of the oral-systemic health concept, which suggests a strong connection between general somatic illness and local inflammatory processes in periodontal tissues, modern medical research is evolving. Chronic generalised periodontitis (CGP) is now recognised as a major modifiable risk factor for the development of cardiovascular diseases (CVD), which continue to be the world's leading cause of death, rather than only a local dental nosology. The World Health Organization estimates that 19% of adults worldwide-more than 1 billion people-have severe forms of periodontitis. In the Republic of Uzbekistan, 47-62% of people over 35 have moderate or severe CGP.

The risk of developing coronary and carotid artery atherosclerosis increases by 1.7-2.3 times, myocardial infarction by 1.4-1.9 times, and cerebral stroke by 1.6-2.1 times in patients with CGP, according to significant epidemiological and meta-analytic studies conducted in recent years (Sanz M. et al., 2020; Tonetti M.S. et al., 2021). Three essential elements make up the pathophysiological link between these pathologies:

- systemic low-grade inflammation (high levels of TNF-α, IL-1β, IL-6, and CRP);
- temporary bacteremia caused by periodontal infections (P. gingivalis, A. actinomycetemcomitans) directly invading the vascular endothelium;
- dyslipidemic shift with reduced apolipoprotein transport.

In cardiological practice, apolipoproteins A1 (ApoA1 - the main anti-atherogenic protein of HDL), B (ApoB - a structural marker of all atherogenic lipoproteins), and E (ApoE - a regulator of lipid clearance) are recognized as more accurate predictors of cardiovascular events than traditional LDL cholesterol.

Precision study of the oral fluid (saliva) proteome is now possible because of the development of mass spectrometry (LC-MS/MS) and multiplex analysis (Luminex xMAP) techniques. Saliva is a perfect substrate for individualised screening since it is non-invasive, safe, and very economical. However, to date, validated proteomic panels for the simultaneous assessment of periodontitis severity and cardiovascular risk are lacking in dental practice, regional reference values for apolipoproteins in saliva for the population of Uzbekistan have not been determined, and algorithms for the interdisciplinary management of such patients have not been implemented.

The study's objectives are to create and validate a personalised treatment for generalised periodontitis and an algorithm based on proteomic profiling of oral fluid for the early prediction of cardiovascular problems in individuals with concurrent cardiovascular disease.

LITERATURE REVIEW

The Oral-Systemic Health Theory: Atherosclerosis and Periodontitis

Chronic generalised periodontitis (CGP) was formerly thought to be an isolated oral illness, but within the last 20 years, periodontal medicine has come to understand it as a powerful cause of systemic vascular disorders [1]. According to seminal epidemiological research and consensus reports from the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP), summarised by Sanz et al. (2020), people with severe periodontitis are 1.7-2.3 times more likely to develop coronary and carotid atherosclerosis [2]. Additionally, intervention studies show that mechanical periodontal treatment improves endothelial function and reduces systemic artery stiffness in a statistically meaningful way, supporting the causal relationships within the paradigm of oral-systemic health [3].

RESEARCH METHODOLOGY

Study Design and Objects

Between 2023 and 2026, the clinical investigation was carried out at the Samarkand Regional Dental Clinic. Three groups of 140 people, ages 45 to 70, were examined:

- **Main Group (n = 65):** Individualised treatment according to salivary proteome profile findings for patients with moderate/severe CGP and concurrent cardiovascular concerns (arterial hypertension, CHD, dyslipidaemia).
- **Comparison Group (n = 45):** Patients with CGP who had conventional therapy in accordance with current therapeutic guidelines without considering proteomic data.
- **Control Group (n = 30):** People of similar age who are in good physical and oral condition.
- **Clinical Dental Block:** Probing depth (PD), clinical attachment level (CAL), PI (Russell), GI (Löe-Silness), and CPITN indicators are calculated at six places per tooth during a standardised examination. The oral hygiene index (OHI-S) and bleeding on probing index (BOP) were assessed. CBCT and digital orthopantomography were used for visualisation.
- **Cardiovascular Block:** SCORE2 and SCORE2-OP charts are used to measure risk. A 12-lead ECG, echocardiography with Doppler, carotid ultrasonography with intima-media thickness (IMT) assessment, 24-hour ambulatory blood pressure monitoring (ABPM), and pulse wave velocity (PWV) measurement were all carried out.

- **Laboratory Biochemical Block (Blood):** ApoE isoforms (\varepsilon2/\varepsilon3/\varepsilon4) using real-time PCR, hs-CRP, fibrinogen, homocysteine, and HbA1c, as well as the lipid profile, serum ApoA1, ApoB, and ApoE using immunoturbidimetry (Cobas Roche).
- **Oral Fluid Proteomic Profiling:** Samples of unstimulated mixed saliva (100–200 µl) were taken only when the stomach was empty. Following centrifugation (3000g \times 15 min), ApoA1, ApoB, and ApoE levels were assessed using ELISA (Abcam) and confirmed by LC-MS/MS mass spectrometry (Orbitrap Fusion, Thermo Scientific). Using the Luminex xMAP platform, multiplex analysis of cytokines (IL-1β, IL-6, IL-8, and TNF-α) was carried out. Additionally, MMP-8, MMP-9, protective salivary proteins (lactoferrin, lysozyme, sIgA), salivary CRP, and oxidative stress indicators (MDA, SOD, GSH) were examined.

ANALYSIS AND RESULTS

Data processing was done using STATISTICA 12.0 and SPSS 26.0 software, as well as R (packages MSstats, limma, ROCR) and Python (scikit-learn, pandas) environments. Spearman/Pearson correlation analyses were used in conjunction with parametric (t-test, ANOVA) and non-parametric (U-test, Kruskal-Wallis) techniques. Prognostic models were constructed using logistic regression with LASSO predictor selection. K-fold cross-validation and bootstrap techniques (1000 iterations) were used to validate the model. ROC curves and AUC calculations were used to assess the models' performance.

Signature of Salivary Lipoproteins

For the first time, regional reference values for apolipoproteins in oral fluid were established for the Republic of Uzbekistan's population during the research. Patients with CGP had a substantial imbalance in their salivary lipid profile, which correlated with blood lipid profile characteristics and the degree of bone tissue loss.

The idea of the "salivary lipoprotein signature of periodontitis" was developed: an early preclinical indicator of systemic lipid homeostasis disruption and periodontal inflammation is a combined increase in ApoB and decrease in ApoA1 in the oral fluid, reaching a ratio coefficient of ApoB/ApoA1 > 1.3. Long before there are noticeable atherosclerotic alterations in the carotid and coronary arteries, this change is seen in saliva.

Risk Prediction and Genetic Markers

The pathogenic relevance of ApoE isoform polymorphism was identified via PCR analysis. The most severe course of generalised periodontitis, high rates of alveolar bone resorption, and worse cardiovascular outcomes have all been linked to the existence of the ApoE-\varepsilon4 variant. High comorbid risk was shown to be independently predicted by ApoE-\varepsilon4.

Eight important predictors from four blocks of characteristics were integrated into a mathematical model for the early prediction of cardiovascular problems using multivariate analysis and LASSO selection (Table 1).

Table 1: **Mathematical Risk Model for Complications Predictors ("PerioCardio-Risk")**

Parameter Block	Identified Predictors
Clinical Periodontal	Bone destruction index (CAL), pocket depth (PD)
Proteomic (Salivary)	ApoB/ApoA1 ratio > 1.3, salivary MMP-8 level
Biochemical (Serum)	High-sensitivity CRP (hs-CRP), serum ApoB level
Behavioral / General	Age, smoking status

With high sensitivity and specificity and an area under the ROC curve (AUC > 0.90), the model showed outstanding operational features. This mathematical solution served as the foundation for the "PerioCardio-Risk" software module in Russian, Uzbek, and English, which calculates risk automatically in less than a second.

Personalised Therapy's Effectiveness

Three distinct protocols-"Classical," "Anti-inflammatory-enhanced" with omega-3 PUFAs and statins, and "Endothelial-protective" with L-arginine, coenzyme Q10, and vitamin D3-were used in our customised algorithm, which demonstrated high clinical efficacy in the main group when compared to the comparison group (Table 2).

Table 2: **Comparative Dynamics of Treatment Efficacy Markers (after 12 months)**

Efficacy Indicator	Main Group (n=65)	Comparison Group (n=45)
Reduction in periodontal pocket depth (PD)	25–35%	10–12%
Normalization of salivary proteomic profile	In 75–85% of patients	In 22–28% of patients
Decrease in salivary pro-inflammatory cytokines	Pronounced ($p < 0.01$)	Insignificant ($p > 0.05$)

The findings clearly demonstrate that oral fluid is a complete reflection of both systemic metabolic problems and the local inflammatory state of periodontal tissues. The idea that lipid problems in CGP are caused by a systemic translocational mechanism is supported by the discovery of high amounts of ApoB and low levels of ApoA1 in saliva. The transcapillary transfer of atherogenic apolipoproteins into the oral fluid seems to be accelerated by oxidative stress and endothelial dysfunction caused by a persistent inflammatory focus in the periodontium.

The found correlation between the severity of CGP and the ApoE-\varepsilon4 isoform is in line with studies from throughout the world on this genotype's function in regulating the macrophage response and lowering cells' ability to reduce inflammation. This creates new opportunities for dental genetic screening.

Multidisciplinary collaboration is a vital component. The suggested method makes it possible to close the gap between main cardiological treatment and dental consultations. This procedure is automated using the "PerioCardio-Risk" program, which gives dentists an evidence foundation for promptly referring patients to a cardiologist two to five years before the clinical manifestation of atherosclerosis (such as myocardial infarction or stroke).

A thorough serological blood test is 1.8-2.2 times more costly than multiplex analysis of saliva for apolipoproteins in a single sample (100-200 µl). This feature, together with the technique's complete non-invasiveness and psychological comfort for the patient, makes it a very useful tool for routine screening in real-world healthcare.

CONCLUSION AND SUGGESTIONS

As a non-invasive diagnostic criterion for coupled periodontal-cardiovascular disease, a novel notion of the "salivary lipoprotein signature of periodontitis" (ApoB/ApoA1 > 1.3) has been established and pathophysiologically validated.

The use of the "PerioCardio-Risk" software's precision mathematical model (AUC > 0.90) guarantees very accurate long-term (2-5 years) prediction of cardiovascular problems.

By using the developed personalised algorithm for differentiated therapy of CGP, it is possible to improve the quality of periodontal rehabilitation (by reducing pocket depth by 25-35%) and restore the oral fluid's metabolic homeostasis in 75-85% of patients, which lowers the burden of systemic inflammation.

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Mas’ul muharrir: Ramzidin Ashurov
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Musahhih: Alibek Zokirov
Sahifalovchi va dizayner: Iskandar Islomov

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