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13.00.00 Pedagogika fanlari
13.00.01 Pedagogika nazariyasi. Pedagogik ta'limotlar tarixi
13.00.02 Ta'lim va tarbiya nazariyasi va metodikasi (sohalar bo'yicha)
13.00.03 Maxsus pedagogika
13.00.04 Jismoniy tarbiya va sport mashg'ulotlari nazariyasi va metodikasi
13.00.05 Kasb-hunar ta'limi nazariyasi va metodikasi
13.00.06 Elektron ta'lim nazariyasi va metodikasi (ta'lim sohalari va bosqichlari bo'yicha)
13.00.07 Ta'limda menejment
13.00.08 Maktabgacha ta'lim va tarbiya nazariyasi va metodikasi
13.00.09 Ijtimoiy pedagogika
07.00.00 Tarix fanlari
19.00.00 Psixologiya fanlari
01.00.00 Fizika-matematika fanlari
02.00.00 Kimyo fanlari
03.00.00 Biologiya fanlari
09.00.00 Falsafa fanlari
10.00.00 Filologiya fanlari
11.00.00 Geografiya fanlari

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A CUSTOMISED METHOD FOR TREATING GENERALISED PERIODONTITIS AND PREDICTING CARDIOVASCULAR PROBLEMS USING SALIVARY PROTEOMIC PROFILING

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Abstract: Chronic generalised periodontitis (CGP) is one recognised modifiable risk factor for cardiovascular diseases (CVD). The use of oral fluid indicators for non-invasive monitoring of concurrent pathology is an intriguing direction in personalised medicine.
Aim of the study. To develop and scientifically test a customised CGP therapy as well as an algorithm based on proteomic profiling of the oral fluid for the early prediction of cardiovascular issues in patients with concomitant pathology.
Methods. There were 140 participants in all (the main group consisted of 65 patients with CGP and cardiovascular risk who received individualised treatment; the comparator group consisted of 45 CGP patients receiving conventional medication; and the control group consisted of 30 healthy individuals). A comprehensive dental, cardiological, and biochemical examination was performed. The proteome profile of saliva (apolipoproteins A1, B, E, and cytokines) was evaluated using ELISA and LC-MS/MS mass spectrometry. In R and Python environments, statistical analysis was performed using LASSO regression and ROC analysis.
Results. The concept of the "salivary lipoprotein signature of periodontitis" (ApoB/ApoA1 ratio in saliva >1.3) as a marker of disruption of systemic lipid homeostasis was validated for the first time. It was shown that the ApoE-ε4 isoform independently predicted worse outcomes. The "PerioCardio-Risk" application incorporates a prognostic model (AUC >0.90). Thanks to individualised care, the salivary profile reverted to normal in 75-85% of patients, and the periodontal pocket depth decreased by 25-35%.
Conclusion. By incorporating salivary proteome profiling into an interdisciplinary approach, it is feasible to improve CGP medication and predict cardiovascular risks two to five years before they manifest clinically.

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

Annotatsiya: Surunkali generalizatsiyalashgan periodontit (SGP) yurak-qon tomir kasalliklari (YQTK) uchun tan olingan o'zgartirilishi mumkin bo'lgan xavf omillaridan biridir. Og'iz suyuqligi ko'rsatkichlaridan hamroh patologiyalarni noinvaziv monitoring qilishda foydalanish shaxsiylashtirilgan tibbiyotning istiqbolli yo'nalishlaridan biri hisoblanadi.

Tadqiqot maqsadi. Hamroh patologiyaga ega bemorlarda og'iz suyuqligining proteomik profillanishiga asoslangan holda yurak-qon tomir muammolarini erta bashorat qilish algoritmini ishlab chiqish va ilmiy jihatdan sinovdan o'tkazish, shuningdek, SGP uchun shaxsiylashtirilgan davolash usulini ishlab chiqish.
Tadqiqot metodlari. Tadqiqotda jami 140 nafar ishtirokchi qatnashdi (asosiy guruh - individual davolash olgan SGP va yurak-qon tomir xavfiga ega 65 nafar bemor; taqqoslash guruhi - an'anaviy davolash olgan 45 nafar SGP bemori; nazorat guruhi - 30 nafar sog'lom shaxs). Keng qamrovli stomatologik, kardiologik va biokimyoviy tekshiruv o'tkazildi. So'lak proteomi profili (A1, B, E apolipoproteinlari 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 markeri sifatida tasdiqlandi. ApoE-ε4 izoformasi noqulay natijalarni mustaqil ravishda bashorat qilishi ko'rsatildi. "PerioCardio-Risk" ilovasiga prognostik model (AUC >0,90) kiritildi. Individual davolash natijasida bemorlarning 75-85 % ida so'lak profili me'yoriga qaytdi, periodontal cho'ntak chuqurligi esa 25-35 % ga kamaydi.
Xulosa. So'lak proteomini profillashni fanlararo yondashuvga kiritish orqali SGPni davolashni takomillashtirish hamda yurak-qon tomir xavflarini ular klinik namoyon bo'lishidan ikki-besh yil oldin bashorat qilish mumkin.

Kalit so'zlar: surunkali generalizatsiyalashgan periodontit, yurak-qon tomir kasalliklari, so'lak proteomik profillanishi, apolipoproteinlar, og'iz suyuqligi biomarkerlari, shaxsiylashtirilgan davolash, yurak-qon tomir xavfini bashorat qilish.

Аннотация: Хронический генерализованный пародонтит (ХГП) является одним из признанных модифицируемых факторов риска сердечно-сосудистых заболеваний (ССЗ). Использование показателей ротовой жидкости для неинвазивного мониторинга сопутствующей патологии является перспективным направлением персонализированной медицины.

Цель исследования. Разработать и научно апробировать персонализированный метод лечения ХГП, а также алгоритм раннего прогнозирования сердечно-сосудистых осложнений у пациентов с сопутствующей патологией на основе протеомного профилирования ротовой жидкости.

Методы исследования. В исследовании приняли участие 140 человек (основную группу составили 65 пациентов с ХГП и сердечно-сосудистым риском, получавших персонализированное лечение; группу сравнения составили 45 пациентов с ХГП, получавших традиционную терапию; контрольную группу составили 30 здоровых лиц). Проведено комплексное стоматологическое, кардиологическое и биохимическое обследование. Протеомный профиль 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 маркера нарушения системного липидного гомеостаза. Показано, что изоформа ApoE-ε4 независимо предсказывает неблагоприятные исходы. В приложение "PerioCardio-Risk" включена прогностическая модель (AUC >0,90). Благодаря персонализированному лечению у 75-85 % пациентов профиль слюны нормализовался, а глубина пародонтальных карманов уменьшилась на 25-35 %.

Заключение. Включение протеомного профилирования слюны в междисциплинарный подход позволяет усовершенствовать лечение ХГП и прогнозировать сердечно-сосудистые риски за два-пять лет до их клинического проявления.

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

NTRODUCTION

Modern medical research is developing within the framework of the oral-systemic health concept, which proposes a significant link between local inflammatory processes in periodontal tissues and overall somatic sickness. Rather than being only a local dental condition, chronic generalised periodontitis (CGP) is now acknowledged as a significant modifiable risk factor for the development of cardiovascular diseases (CVD), which remain the leading cause of death worldwide. According to estimates from the World Health Organization, over 1 billion individuals, or 19% of adults globally, suffer from severe types of periodontitis. In the Republic of Uzbekistan, 47-62% of adults over 35 have moderate or severe CGP.

Significant epidemiological and meta-analytic studies carried out in recent years have shown that patients with CGP have an increased risk of developing coronary and carotid artery atherosclerosis by 1.7-2.3 times, myocardial infarction by 1.4-1.9 times, and cerebral stroke by 1.6-2.1 times (Sanz M. et al., 2020; Tonetti M.S. et al., 2021). The pathophysiological connection between these illnesses consists of three fundamental components:

- transient bacteremia brought on by periodontal infections (P. gingivalis, A. actinomycetemcomitans) that directly invade the vascular endothelium;
- dyslipidemic shift with decreased apolipoprotein transport;
- systemic low-grade inflammation (high levels of TNF-α, IL-1β, IL-6, and CRP).

Apolipoproteins A1 (ApoA1, the primary anti-atherogenic protein of HDL), B (ApoB, a structural marker of all atherogenic lipoproteins), and E (ApoE, a regulator of lipid clearance) are known to be more reliable predictors of cardiovascular events than conventional LDL cholesterol in cardiological practice.

The advancement of mass spectrometry (LC-MS/MS) and multiplex analysis (Luminex xMAP) methods has made it feasible to analyse the oral fluid (saliva) proteome with precision. Due to its non-invasiveness, safety, and affordability, saliva is an ideal substrate for personalised screening. However, regional reference values for apolipoproteins in saliva for the Uzbek population have not yet been established, algorithms for the interdisciplinary management of such patients have not been put into place, and validated proteomic panels for the simultaneous assessment of periodontitis severity and cardiovascular risk are lacking in dental practice.

The project aims to develop and test an algorithm based on proteomic profiling of oral fluid for the early prediction of cardiovascular issues in people with concomitant cardiovascular illness, as well as a customised therapy for generalised periodontitis.

LITERATURE REVIEW

The Theory of Oral-Systemic Health: Periodontitis and Atherosclerosis

In the last 20 years, periodontal medicine has evolved to recognise chronic generalised periodontitis (CGP) as a potent cause of systemic vascular problems. Previously, CGP was believed to be an isolated oral disease [1]. People with severe periodontitis are 1.7-2.3 times more likely to develop coronary and carotid atherosclerosis, according to groundbreaking 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) [2]. Furthermore, intervention studies demonstrate that mechanical periodontal therapy statistically significantly lowers systemic arterial stiffness and enhances endothelial function, validating the causal links within the paradigm of oral-systemic health [3].

RESEARCH METHODOLOGY

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:** During a standardised examination, six locations per tooth are used to compute probing depth (PD), clinical attachment level (CAL), PI (Russell), GI (Löe-Silness), and CPITN indices. Both the bleeding on probing index (BOP) and the oral hygiene index (OHI-S) were evaluated. For visualisation, digital orthopantomography and CBCT were used.
- **Cardiovascular Block:** Risk is assessed using SCORE2 and SCORE2-OP charts. A 24-hour ambulatory blood pressure monitoring (ABPM), 12-lead ECG, echocardiography with Doppler, carotid ultrasonography with intima-media thickness (IMT) evaluation, and pulse wave velocity (PWV) measurement were all performed.
- **Laboratory Biochemical Block (Blood):** The lipid profile, serum ApoA1, ApoB, and ApoE using immunoturbidimetry (Cobas Roche), and ApoE isoforms (\varepsilon2/\varepsilon3/\varepsilon4) using real-time PCR, hs-CRP, fibrinogen, homocysteine, and HbA1c.
- **Oral Fluid Proteomic Profiling:** Only when the stomach was empty were samples of unstimulated mixed saliva (100-200 µl) collected. ApoA1, ApoB, and ApoE levels were measured by ELISA (Abcam) and verified by LC-MS/MS mass spectrometry (Orbitrap Fusion, Thermo Scientific) after centrifugation (3000g \ times 15 min). Multiplex analysis of cytokines (IL-1β, IL-6, IL-8, and TNF-α) was performed using the Luminex xMAP platform. MMP-8, MMP-9, salivary CRP, oxidative stress markers (MDA, SOD, GSH), and protective salivary proteins (lactoferrin, lysozyme, and sIgA) were also investigated.

ANALYSIS AND RESULTS

STATISTICA 12.0, SPSS 26.0, R (packages MSstats, limma, ROCR), and Python (scikit-learn, pandas) environments were used for data processing. Both parametric (t-test, ANOVA) and non-parametric (U-test, Kruskal-Wallis) methods were used with Spearman/Pearson correlation analysis. Logistic regression with LASSO predictor selection was used to build prognostic models. The model was validated using bootstrap approaches (1000 iterations) and K-fold cross-validation. The models' performance was evaluated using ROC curves and AUC computations.

Salivary Lipoprotein Signature

During the study, regional reference values for apolipoproteins in oral fluid were established for the first time for the people of the Republic of Uzbekistan. The degree of bone tissue loss and blood lipid profile features were connected with a significant imbalance in salivary lipid profiles in patients with CGP.

The concept of the "salivary lipoprotein signature of periodontitis" was created: a combined increase in ApoB and a decrease in ApoA1 in the oral fluid, reaching a ratio coefficient of ApoB/ApoA1 > 1.3, is an early

preclinical indicator of systemic lipid homeostasis disruption and periodontal inflammation. Saliva exhibits this shift long before the carotid and coronary arteries show obvious signs of atherosclerosis.

Genetic Markers and Risk Prediction

PCR analysis was used to determine the pathogenic significance of ApoE isoform polymorphism. The presence of the ApoE-\varepsilon4 variation has been associated with poorer cardiovascular outcomes, high rates of alveolar bone resorption, and the most severe course of generalised periodontitis. ApoE-\varepsilon4 was shown to be an independent predictor of high comorbid risk.

Using multivariate analysis and LASSO selection, eight significant predictors from four blocks of data were included in a mathematical model for the early prediction of cardiovascular issues (Table 1).

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

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

The model demonstrated exceptional operational characteristics with high sensitivity and specificity and an area under the ROC curve (AUC > 0.90). The "PerioCardio-Risk" software module in Russian, Uzbek, and English, which computes risk automatically in less than a second, was built around this mathematical solution.

The Efficiency of Personalised Therapy

Our customised algorithm used three different protocols: "Classical," "Anti-inflammatory-enhanced" with omega-3 PUFAs and statins, and "Endothelial-protective" with L-arginine, coenzyme Q10, and vitamin D3. The main group showed high clinical efficacy in comparison to the comparison group (Table 2).

Table 2: **Comparative Dynamics of Treatment Effectiveness 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 results unequivocally show that both the local inflammatory state of periodontal tissues and systemic metabolic disorders are fully reflected in oral fluid. The finding of high levels of ApoB and low levels of ApoA1 in saliva supports the theory that lipid issues in CGP are brought on by a systemic translocational mechanism. Oxidative stress and endothelial dysfunction brought on by a prolonged inflammatory focus in the periodontium seem to hasten the transcapillary transfer of atherogenic apolipoproteins into the oral fluid.

The observed association between the degree of CGP and the ApoE-\varepsilon4 isoform is consistent with research conducted worldwide on the role of this genotype in controlling the macrophage response and reducing cells' capacity to decrease inflammation. For oral genetic screening, this opens up new possibilities.

Multidisciplinary cooperation is essential. Closing the gap between primary cardiological care and dental visits is made feasible by the recommended approach. The "PerioCardio-Risk" technology automates this process and provides dentists with evidence to rapidly send patients to a cardiologist two to five years prior to the critical atherosclerotic presentation (such as myocardial infarction or stroke).

Multiplex analysis of saliva for apolipoproteins in a single sample (100–200 µl) is 1.8-2.2 times less expensive than a comprehensive serological blood test. This characteristic, together with the technique's total non-invasiveness and psychological comfort for the patient, makes it a very helpful tool for regular screening in actual healthcare settings.

CONCLUSION AND SUGGESTIONS

The unique concept of the "salivary lipoprotein signature of periodontitis" (ApoB/ApoA1 > 1.3) has been developed and pathophysiologically verified as a non-invasive diagnostic criterion for linked periodontal-cardiovascular illness.

The precise mathematical model (AUC > 0.90) used by the "PerioCardio-Risk" program ensures extremely accurate long-term (2-5 years) prediction of cardiovascular issues.

In 75-85% of patients, the developed personalised algorithm for differentiated therapy of CGP can improve the quality of periodontal rehabilitation (by reducing pocket depth by 25-35%) and restore the metabolic homeostasis of the oral fluid, which reduces the burden of systemic inflammation.

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13.00.00 Pedagogika fanlari
13.00.01 Pedagogika nazariyasi. Pedagogik ta’limotlar tarixi
13.00.02 Ta’lim va tarbiya nazariyasi va metodikasi (sohalar bo‘yicha)
13.00.03 Maxsus pedagogika
13.00.04 Jismoniy tarbiya va sport mashg‘ulotlari nazariyasi va metodikasi
13.00.05 Kasb-hunar ta’limi nazariyasi va metodikasi
13.00.06 Elektron ta’lim nazariyasi va metodikasi (ta’lim sohalari va bosqichlari bo‘yicha)
13.00.07 Ta’limda menejment
13.00.08 Maktabgacha ta’lim va tarbiya nazariyasi va metodikasi
13.00.09 Ijtimoiy pedagogika
07.00.00 Tarix fanlari
19.00.00 Psixologiya fanlari
01.00.00 Fizika-matematika fanlari
02.00.00 Kimyo fanlari
03.00.00 Biologiya fanlari
09.00.00 Falsafa fanlari
10.00.00 Filologiya fanlari
11.00.00 Geografiya fanlari

MAKTABGACHA VA MAKTAB TA’LIMI

Mas’ul muharrir: Ramzidin Ashurov
Ingliz tili muharriri: Murod Xoliyorov
Musahhih: Alibek Zokirov
Sahifalovchi va dizayner: Iskandar Islomov

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“Maktabgacha va maktab ta’limi” jurnali 26.09.2023-yildan
O‘zbekiston Respublikasi Prezidenti Adminstratsiyasi huzuridagi
Axborot va ommaviy kommunikatsiyalar agentligi tomonidan
№C–5669363 reyestr raqami tartibi bo‘yicha ro‘yxatdan o‘tkazilgan.
Litsenziya raqami: № 136361.

Manzilimiz: Toshkent shahar, Yunusobod tumani
19-mavze, 17-uy.