

**DORI VOSITALARI BILAN BOG'LIQ JAG' SUYAKLARI
OSTEONEKROZINI (MRONJ) ERTA ANIQLASHDA SO'LAK
BIOMARKERLARINING DIAGNOSTIK AHAMIYATI****G'afforova Hojaroy Panji qizi**

Termiz iqtisodiyot va servis universiteti stomatologiya mutaxassisligi magistranti

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Maqolada dori vositalari bilan bog'liq jag' suyaklari osteonekrozini (medication-related osteonecrosis of the jaw, MRONJ) erta aniqlashda so'lak biomarkerlarining diagnostik ahamiyati zamonaviy dalillar asosida baholandi. Tadqiqot birlamchi klinik tajriba emas, balki sistematik sharhlar, metabolomik va proteomik case-control tadqiqotlar, AAOMS va MASCC/ISOO klinik hujjatlari hamda O'zbekiston stomatologik adabiyotlariga tayangan ikkilamchi dalillar sintezidir. 2023-yilgi sistematik sharhda 765 manbadan 10 ta maqola kiritilib, jami 272 MRONJ holati tahlil qilingan; so'lak oqimi kamayishi, mikrobiom va cytokine profilidagi o'zgarishlar, interleykinlar, hypotaurine va oqsil tarkibidagi siljishlar MRONJ bilan bog'langan. 2023-yilgi quantitative salivary proteomics proof-of-concept tadqiqotida 38 ta so'lak namunasi (18 MRONJ, 10 bone-modifying agent qabul qiluvchi nazorat, 10 sog'lom nazorat) tahlil qilinib, 586 ta oqsil aniqlangan; MMP9–AACT–HBD uchlik biomarker paneli AUC 0,879, sezgirlik 90% va spetsifiklik 78,9% ko'rsatgan. Metabolomik tadqiqotda MRONJ bemorlarining so'lagida hypotaurine konsentratsiyasi 2,28 baravar oshgan. 2024-yilgi proteomik ishda 1545 differensial oqsil aniqlanib, 43 tasi yuqori va 11 tasi past regulyatsiyalangan; APOA2, APOB, APOE, C4B, FGG, HP va SERPIND1 kabi hub-oqsillar ajratilgan. 2026-yilgi protein-signature meta-tahlili APOB, APOA2 va SERPIND1ning oshgan so'lak darajalarini MRONJ bilan bog'lagan. Biroq hozircha hech bir so'lak biomarkeri yoki paneli mustaqil klinik tashxis uchun validatsiyalangan standart hisoblanmaydi. So'lak biomarkerlarining eng maqbul roli yuqori xavfli bemorlarni skrining qilish, klinik va radiologik tekshiruvni kuchaytirish hamda davolash monitoringini to'ldirishdan iborat.

Kalit so'zlar: MRONJ, jag' osteonekrozi, so'lak biomarkerlari, MMP9, hypotaurine, proteomika, metabolomika, APOB, interleykin-8, erta tashxis.

АННОТАЦИЯ

В статье оценивается диагностическое значение слюнных биомаркеров для раннего выявления медикаментозно-ассоциированного остеонекроза челюстей (MRONJ). Работа представляет собой синтез вторичных доказательств на основе систематических обзоров, метаболомных и протеомных исследований, клинических документов AAOMS и MASCC/ISOO, а также стоматологических публикаций, используемых в Узбекистане. Систематический обзор 2023 года включил 10 исследований и 272 случая MRONJ и выявил связь заболевания с уменьшением слюноотделения, изменениями микробиома, цитокинов, интерлейкинов, гипотаурина и белкового профиля слюны. В исследовании количественной протеомики 38 образцов слюны было идентифицировано 586 белков, а панель MMP9–AACT–HBD показала AUC 0,879, чувствительность 90% и специфичность 78,9%. В метаболомном исследовании концентрация гипотаурина в слюне при MRONJ была повышена в 2,28 раза. Протеомное исследование 2024 года выявило 1545 дифференциально экспрессируемых белков, включая 43 повышенных и 11 сниженных при заданном пороге. Несмотря на перспективность, ни один слюнный биомаркер пока не признан самостоятельным надежным клиническим тестом для MRONJ.

Ключевые слова: MRONJ, остеонекроз челюсти, слюнные биомаркеры, MMP9, гипотаурин, протеомика, метаболомика, АРОВ, интерлейкин-8, ранняя диагностика.

ABSTRACT

This article evaluates the diagnostic significance of salivary biomarkers for the early detection of medication-related osteonecrosis of the jaw (MRONJ). The study is a secondary evidence synthesis based on systematic reviews, metabolomic and proteomic case-control studies, AAOMS and MASCC/ISOO clinical documents, and selected dental literature relevant to Uzbekistan. A 2023 systematic review included 10 eligible studies and 272 MRONJ cases and associated the disease with reduced salivary flow and changes in the salivary microbiome, cytokine/interleukin profiles, hypotaurine, and protein signatures. In a quantitative salivary proteomics proof-of-concept study using 38 unstimulated saliva samples (18 MRONJ, 10 bone-modifying-agent users without MRONJ, and 10 healthy controls), 586 proteins were quantified; an optimized MMP9–AACT–HBD panel achieved AUC 0.879, sensitivity 90%, and specificity 78.9%. Metabolomic profiling demonstrated a 2.28-fold increase in salivary hypotaurine in a validation cohort. A 2024 salivary proteomics study identified 1,545 differentially expressed proteins, including 43 significantly upregulated and 11

downregulated proteins at a 1.5-fold cutoff and adjusted $p < 0.05$, with hub proteins related to lipoprotein metabolism, innate immunity, complement, and coagulation. A 2026 systematic review and meta-analysis further reported increased salivary APOB, APOA2, and SERPIND1 in MRONJ. Despite these promising findings, no salivary biomarker or biomarker panel has yet been established as a validated standalone clinical diagnostic test. Their most realistic near-term role is adjunctive risk stratification, triggering intensified clinical/radiologic evaluation, and longitudinal monitoring.

Keywords: MRONJ, jaw osteonecrosis, salivary biomarkers, MMP9, hypotaurine, proteomics, metabolomics, APOB, interleukin-8, early diagnosis.

KIRISH

MRONJ antiresorptiv, antiangiogen va ayrim boshqa dori vositalarini qabul qilgan bemorlarda rivojlanishi mumkin bo'lgan kam uchraydigan, biroq og'ir stomatologik asoratdir. AAOMS 2022 mezonlariga ko'ra tashxis odatda maxillofasial sohada sakkiz haftadan ortiq davom etuvchi ochiq suyak yoki fistula orqali zondlanadigan suyak, MRONJ bilan bog'liq dori ekspozitsiyasi va jag'larga radioterapiya yoki metastatik kasallik tarixining yo'qligi kombinatsiyasiga asoslanadi.

MRONJ klinik jihatdan kech aniqlanishi mumkin, chunki erta bosqichlarda bemorda ochiq suyak bo'lmazligi, faqat noaniq og'riq, periodontal yoki periapikal simptomlar, fistula, tish mobiliteti yoki radiologik o'zgarishlar kuzatilishi mumkin. Erta diagnostika jarrohlik hajmini kamaytirish, infeksiyani nazorat qilish va hayot sifatini saqlash uchun katta ahamiyatga ega.

Hozirgi klinik amaliyotda MRONJ uchun alohida, ishonchli laborator biomarker mavjud emas. 2024-yilgi biomarker scoping reviewda CTX, BAP, PTH, osteocalcin, P1NP, NTX, IL-6, CRP va boshqa ko'plab markerlar tahlil qilingan bo'lsa-da, birortasi MRONJ rivojlanishini ishonchli bashorat qiluvchi klinik standart darajasiga yetmagan.

CTX uzoq vaqt MRONJ xavfini baholash uchun muhokama qilingan. Biroq 2025-yilgi sistematik sharh va meta-tahlil hamda 2026-yilgi Asia-Pacific consensus systemic CTXning oral surgery oldidan MRONJ xavfini ishonchli predict qilish uchun yetarli emasligini ta'kidlaydi. Shu sababli tadqiqot e'tibori mahalliy biologik muhitni bevosita aks ettirishi mumkin bo'lgan so'lak biomarkerlariga ko'chmoqda.

So'lak invaziv bo'lmagan, takroriy va nisbatan arzon biologik material hisoblanadi. U oral mucosa, periodontal to'qimalar, mikrobiom, yallig'lanish, fermentlar, metabolitlar va tizimli kasalliklarning ayrim molekulyar izlarini o'zida aks ettiradi. MRONJ jag'

suyagi, yumshoq to'qima, immunitet va infeksiya o'rtasidagi murakkab jarayon bo'lgani uchun saliva proteomics va metabolomics nazariy jihatdan ayniqsa jozibador.

2023-yilgi sistematik sharh dori vositalari fonida so'lak oqimining kamayishi va salivary cytokine, interleukin, microbiome, metabolite va protein profillarining o'zgarishini MRONJ bilan bog'lagan. Biroq kiritilgan tadqiqotlar soni atigi 10 ta, MRONJ holatlari 272 ta bo'lgani va metodologik heterojenlik yuqori bo'lgani sabab xulosalar ehtiyotkorlik bilan talqin qilinishi kerak.

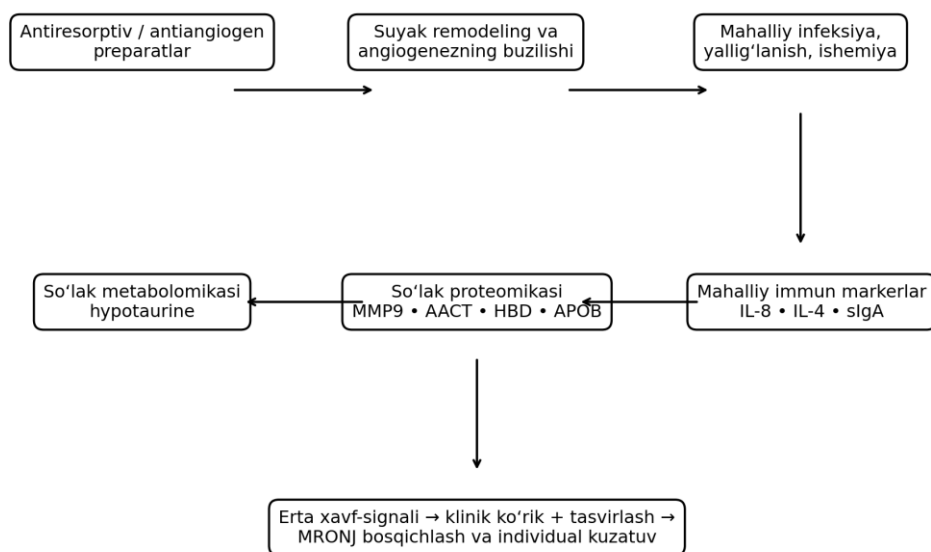
Proteomik yondashuvlar so'lakdagi yuzlab yoki minglab oqsillarni bir vaqtning o'zida o'lchash imkonini beradi. Lorenzo-Pouso va hammualliflar MRONJda MMP8, MMP9, A1BG, AACT, HBB va HBD kabi oqsillarni istiqbolli nomzodlar sifatida ajratgan. Ularning optimallashtirilgan MMP9–AACT–HBD paneli diagnostik diskriminatsiya uchun AUC 0,879 ko'rsatgan.

Metabolomik tadqiqotlar esa kichik molekulali metabolitlarni baholaydi. Yatsuoka va hammualliflar salivary hypotaurine MRONJda 2,28 baravar oshishini ko'rsatgan va uni erta detection marker sifatida taklif qilgan. Ushbu natija biologik jihatdan yallig'lanish va bakterial jarayonlar bilan bog'liq bo'lishi mumkin.

O'zbekistonda MRONJga klinik qiziqish oshmoqda. 2026-yilda Minnulin, Rakhimberdiev, Mirzaqulov, Tursunov va Urazov prostata saratoni suyak metastazlarida bisfosfonat terapiyasi fonidagi MRONJning unresolved diagnostik va terapevtik muammolarini tahlil qilgan. Mahalliy stomatologik ilmiy maktabda og'iz suyuqligi biokimyoviy va immun markerlarini diagnostik maqsadda o'rganish bo'yicha ham ishlar mavjud.

Tadqiqotning maqsadi — MRONJni erta aniqlashda so'lak biomarkerlarining zamonaviy diagnostik salohiyatini tizimlashtirish, metabolomik, proteomik va mahalliy immun markerlarni qiyoslash, mavjud statistik dalillarni umumlashtirish hamda klinik amaliyotga integratsiya qilishning ehtiyotkor modelini taklif etish.

MRONJni erta aniqlashda so‘lak biomarkerlaridan foydalanish modeli



1-rasm. MRONJni erta aniqlashda so‘lak biomarkerlarini klinik tekshiruv va tasvirlash bilan integratsiya qilish modeli.

Asosiy qism

Ushbu maqola birlamchi klinik tadqiqot emas, balki ikkilamchi dalillar sintezidir. Asosiy manbalar sifatida MRONJ va saliva o‘rtasidagi munosabatni baholagan sistematik sharhlar, salivary proteomics va metabolomics case-control tadqiqotlari, biomarker scoping reviewlar, AAOMS position paper, MASCC/ISOO clinical practice statement va O‘zbekiston manbalari tanlandi.

Dalillar biomarker turi bo‘yicha to‘rt guruhga ajratildi: (1) metabolomik markerlar — hypotaurine va boshqa kichik metabolitlar; (2) proteomik markerlar — MMP8/MMP9, AACT, HBD, APOB, APOA2, SERPIND1 va boshqa oqsillar; (3) mahalliy immun markerlar — IL-8, IL-4, sIgA, IgM; (4) suyak metabolizmi markerlari — NTX, BAP va sistemik CTX bilan bog‘liq dalillar.

2023-yilgi sistematik sharh PubMed, Web of Science, Cochrane va Embase bazalaridan 765 ishni topib, 10 ta maqolani kiritgan. Jami 272 MRONJ holati tahlil qilingan, bemorlarning o‘rtacha yoshi 66 yil bo‘lgan. Dori vositalari fonidagi so‘lak oqimi kamayishi, microbiome va cytokine profili, interleykinlar, hypotaurine va binding-protein o‘zgarishlari MRONJ bilan bog‘langan.

Lorenzo-Pouso va hammualliflarning proteomik case-control tadqiqotida 38 ta unstimulated whole saliva namunasi olingan: 18 MRONJ bemori, 10 bone-modifying agent qabul qiluvchi MRONJsiz nazorat va 10 sog‘lom shaxs. SWATH-MS bilan 586

ta oqsil kvantifikatsiya qilingan, MRONJ va nazoratlar orasida 175 ta oqsil sezilarli farq ko'rsatgan. MMP9, AACT va HBDdan tuzilgan uchlik panel ROC tahlilida AUC 0,879, sensitivity 90% va specificity 78,9% ko'rsatgan.

Yatsuoka va hammualliflarning metabolomik ishida 17 MRONJ bemori ishtirok etgan. Screening bosqichida stage ≥ 1 MRONJ (n=9) nazorat bilan, validation bosqichida qo'shimcha stage ≥ 1 MRONJ (n=8) kimyoterapiyadan keyingi MRONJsiz nazorat (n=9) bilan qiyoslangan. Validationda salivary hypotaurine 2,28-fold oshgani tasdiqlangan.

2024-yilgi LC-MS/MS salivary proteomics tadqiqotida 10 MRONJ va 10 nazorat shaxs tahlil qilingan. Umumiy 1545 differentially expressed proteins qayd etilib, 1,5-fold cutoff va adjusted $p < 0,05$ bo'yicha 43 ta oqsil yuqori va 11 ta past regulatsiyalangan. Bioinformatik tahlil lipid metabolism, innate immunity, complement va coagulation pathwaysni ustuvor biologik yo'llar sifatida ko'rsatgan.

2026-yilgi systematic review va meta-analysis uchta proteomik tadqiqotni kiritib, ikkitasini meta-tahlil qilgan. MRONJ bemorlarida salivary APOB, APOA2 va SERPIND1 yuqoriligi, KRT16 esa pasayish tendensiyasini ko'rsatgani qayd etilgan. Tadqiqotlar sonining kichikligi va heterojenlik klinik threshold ishlab chiqishga hali imkon bermaydi.

Og'iz suyuqligidagi mahalliy immun markerlar ham biologik asosga ega. Yaremenko va hammualliflar MRONJ bemorlarida IL-8, IL-4, sIgA va IgM oshishini ko'rsatgan. Ushbu markerlar infeksiya-yallig'lanish komponentini aks ettiradi, ammo ular MRONJga mutlaq spesifik emas va periodontal yoki boshqa oral inflammatory kasalliklarda ham oshishi mumkin.

Biomarker natijalarini talqin qilishda preanalitik omillar muhim: saliva stimulated/unstimulated bo'lishi, sutkalik ritm, ovqat, oral hygiene, qon kontaminatsiyasi, flow rate, cancer status, chemotherapy, periodontal inflammation va sample storage diagnostik signalga ta'sir qiladi. Shu sababli kelgusi klinik testlar standart saliva-collection protokoliga ega bo'lishi kerak.

Biomarker yo'nalishi	Tadqiqot/dalil	Asosiy natija	Klinik talqin
Proteomik panel	38 saliva sample; 18 MRONJ	MMP9–AACT– HBD: AUC 0,879; Se 90%; Sp 78,9%	Eng aniq e'lon qilingan diagnostik panel; validation talab qiladi.

Biomarker yoʻnalishi	Tadqiqot/dalil	Asosiy natija	Klinik talqin
Metabolomika	17 MRONJ bemori	Hypotaaurine validationda 2,28-fold oshgan	Erta detection uchun istiqbolli kichik metabolit.
Proteomika 2024	10 MRONJ + 10 control	1545 DEP; 43 up, 11 down	Lipoprotein, innate immunity, complement/coagulation yoʻllari.
Protein meta- analysis 2026	3 study; 2 meta- analysis	APOB, APOA2, SERPIND1 yuqori	Non-invasive screening uchun exploratory signal.
Mahalliy immun markerlar	25 MRONJ + 23 control	IL-8, IL-4, sIgA, IgM oshgan	Inflammatory activityni aks ettiradi, spesifikligi cheklangan.

1-jadval. MRONJ uchun asosiy soʻlak biomarker yoʻnalishlari va ularning dalillari.

XULOSA

Soʻlak biomarkerlari MRONJni erta aniqlash uchun istiqbolli, invaziv boʻlmagan diagnostik yoʻnalishdir, biroq hozircha mustaqil klinik standart emas.

Eng kuchli eʼlon qilingan diagnostik signal MMP9–AACT–HBD proteomik panelida kuzatilgan: AUC 0,879, sensitivity 90% va specificity 78,9%. Ushbu natija screening uchun umidli, ammo external validationni talab qiladi.

Salivary hypotaaurine MRONJda 2,28 baravar oshgani metabolomik early-marker konsepsiyasini qoʻllab-quvvatlaydi. Biroq cutoff, specificity va boshqa oral inflammatory kasalliklardan ajratish qobiliyati hali toʻliq oʻrganilmagan.

2024–2026 proteomik ishlar APOB, APOA2, SERPIND1, complement va coagulation bilan bogʻliq oqsillarni MRONJ molecular signatureining muhim komponentlari sifatida koʻrsatmoqda.

IL-8, IL-4, sIgA va IgM kabi ogʻiz suyuqligi immun markerlarining oshishi MRONJdagi mahalliy yalligʻlanish va immun dysregulationni aks ettiradi, lekin ularning MRONJga spesifikligi cheklangan.

CTX va boshqa systemic bone-turnover markerlari MRONJ xavfini mustaqil predict qilish uchun ishonchli emas. Kelajak multi-omics va multimarker panel, standardized saliva collection va independent multicenter validationga bogʻliq.

Amaliyotda soʻlak biomarker natijasi dori tarixi, klinik simptomlar, exposed/probeable bone, radiografik/CBCT tekshiruv va differential diagnosis bilan birga talqin qilinishi lozim.

Oʻzbekistonda antiresorptiv preparat qabul qiluvchi bemorlarda prospective saliva biobank va multicenter biomarker validation tashkil etish MRONJni erta aniqlash algoritmini yaratish uchun eng muhim keyingi qadamdir.

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