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AUTOIMMUN YALLIG'LANISH - PARODONTIT VA ATEROSKLEROZ O'RTASIDAGI SABABIY BOG'LIQLIK SIFATIDA

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ANNOTATSIYA

So'ngi bir necha yil ichida surunkali yurak kasalligi, o'tkir koronar sindrom, arterial gipertenziya va metabolik sindrom bilan har xil og'irlikdagi parodontit o'rtasidagi bog'liqlikni aniqlashga qaratilgan yetarli miqdordagi randomizatsiyalangan klinik tadqiqotlar o'tkazildi. Bunda yurak kasalliklarining deyarli barchasi ateroskleroz fonida rivojlanadi. Parodontit va turli joylarda joylashgan ateroskleroz o'rtasidagi umumiylik hali ham aniqlanishi kerak va ushbu sharh hozirgi kunga qadar olib borilgan tadqiqotlarni umumlashtirish uchun mo'ljallangan.

Kalit so'zlar. Parodontit, ateroskleroz, yallig'lanishga qarshi sitokinlar.

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АУТОИММУННОЕ ВОСПАЛЕНИЕ – КАК ПРИЧИННО-СЛЕДСТВЕННАЯ СВЯЗЬ ПАРОДОНТИТА И АТЕРОСКЛЕРОЗА

АННОТАЦИЯ

Последние несколько лет достаточное количество рандомизированных клинических исследований направлено на поиски связей заболеваний пародонта, в частности, пародонтита различной степени тяжести с хронической ишемической болезни сердца, острого коронарного синдрома, артериальной гипертонией и метаболического синдрома. Практически все эти кардиологические заболевания развиваются на фоне атеросклероза. Общее между пародонтитом и атеросклерозом различных локализаций предстоит еще выяснить и этот обзор посвящен обобщению исследований на данный момент и которые еще предстоят в будущем.

Ключевые слова. Пародонтит, атеросклероз, провоспалительные цитокины.

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AUTOIMMUNE INFLAMMATION - AS A CAUSAL RELATIONSHIP BETWEEN PERIODONTITIS AND ATHEROSCLEROSIS

ANNOTATION

Over the past few years, a sufficient number of randomized clinical trials have been aimed at finding links between periodontal diseases, in particular, periodontitis of varying severity with chronic coronary heart disease, acute coronary syndrome, arterial hypertension and metabolic syndrome. Almost all of these cardiac diseases develop against the background of atherosclerosis. The commonality between periodontitis and atherosclerosis of various localizations remains to be elucidated, and this review is intended to summarize the research to date and that is still to come in the future.

Keywords. Periodontitis, atherosclerosis, pro-inflammatory cytokines.

Deyarli barcha yurak-qon tomir kasalliklarining asosiy sababi aterosklerozdir. Ateroskleroz - surunkali yallig'lanishli tomir kasalligi bo'lib, aterosklerotik blyashka hosil qilish uchun intimada lipidlarning cho'kishiga olib keladi (1,3). Blyashka ko'payishi va o'sishi tomirlarning torayishi buning natijasida qon oqimini pasayishiga olib keladi, bu deyarli barcha organlar va to'qimalarning ishemiyasiga olib keladi.

Blyashka yorilishi qon tomirlarining trombozi va tanadagi qaytarilmas jarayonlarga olib kelishi mumkin. Ateroskleroz bilan bog'liq bo'lgan asosiy yurak kasalliklariga miyokard infarkti (o'limga olib keladigan va o'limga olib kelmaydigan), stenokardiya, o'tkir koronar sindrom, aritmiya, surunkali yurak etishmovchiligi, yurak klapanlari kasalliklari va kardiyomiyopatiya kiradi (2). Aterosklerozdan ta'sirlangan asosiy tomirlar koronar, uyqu arteriyasi, periferik arteriyalar,

Butun dunyoda yurak-qon tomir kasalliklari yigirma yil muqaddam o'limning asosiy sababi bo'lib, hozirda bemorlarni davolashga yuqori darajada rioya qilishiga qaramay, ko'p sonli turli xil dori-darmonlar va turli xil interventsion aralashuvlar - qon tomirlarini stentlash va koronar arteriyalarni shuntlash. Biz o'zgartirishimiz mumkin bo'lgan ko'plab o'zgartirilishi mumkin bo'lgan xavf omillari va ateroskleroz bilan bog'liq o'zgartirilmaydigan xavf omillari, xususan, yuqori tana massasi indeksi, semizlik, qandli diabet, insulin, qon bosimi, harakatsiz turmush tarzi, umumiy xolesterin va past zichlikdagi lipoproteinlarning yuqori darajasi. Aterosklerozning o'zi doimiy yallig'lanish bilan birga keladi va tomirlar bilan bevosita bog'liq bo'lmagan parodontal kasalliklar tanadagi autoimmun yallig'lanishni doimo qo'llab-quvvatlashini aniqlash kerak. Ateroskleroz- bu immunitet reaktsiyasiga javoban qon tomirlarining endotelial qoplamasi va silliq mushak hujayralari (SMH) qatlamlari o'rtasida joylashgan tomir intimasining fokal qalinlashuvidir (14). Endotelial disfunktsiya aterosklerotik shakllanishning eng erta o'zgarishidir. Aterosklerozning asosiy etiologiyasi noma'lum (15). Shu bilan birga, ushbu patologiyaning rivojlanishiga boshqa xavf omillari sezilarli darajada hissa qo'shadi, masalan, plazmadagi xolesterin profilining anormalligi, chekish, gipertenziya, diabet va yallig'lanish vositachilarining, shu jumladan CRO va sitokinlarning yuqori darajalari (15). So'nggi yillarda tadqiqotchilar aterosklerozning eng dayshatli asoratlari - miokard infarktining rivojlanishida immunitet omillarining, xususan, sitokinlar kaskadining roli bilan tobora ko'proq qiziqishmoqda (4,13). Yallig'lanish va aterosklerozning umumiyligi juda tabiiy, chunki ikkala sindrom ham biriktiruvchi to'qimalarning bir xil hujayralarini hosil qiladi: endotelial va silliq mushak hujayralari (SMH), fibroblastlar, monotsitlar va makrofaglar, neytrofillar, trombotsitlar va kamroq darajada T- va B. -limfotsitlar (3). So'nggi yillarda tadqiqotchilar aterosklerozning eng og'ir asorati - miyokard infarkti rivojlanishida immunitet omillari, xususan, yallig'lanishga qarshi sitokinlarning roli bilan tobora ko'proq qiziqishmoqda (8).

Ateroskleroz past zichlikdagi lipoproteinlar (PZL) intimada to'planishi bilan boshlanadi, ular oksidlanadi. Bu, o'z navbatida, ICAM-1, qon tomir hujayra yopishish molekulasi-1 (VCAM-1) va selektinlar (VCAM-1) kabi hujayra yuzasi oqsillarining yaqin atrofdagi endotelial hujayralarida ko'payishini faollashtiradi.(15). Aylanib yuruvchi yallig'lanish hujayralarining (monotsitlar, limfotsitlar) molekulalariga yopishishi ularning intimaning yallig'langan joyiga diapedezlanishi tufayli kuchayadi (15). Aterosklerotik o'zgarishlarning dastlabki rivojlanishi monotsitlarning makrofaglarga differensiallanishi natijasida yuzaga keladi, ular PZL ni yutib, ko'pikli hujayralarni, keyin esa yog'li chiziqlarni hosil qiladi (15,16). Keyinchalik, T-leykotsitlar INF-Y, TNF-a va IL-1e kabi yallig'lanish sitokinlarining ko'payishi bilan hujayra vositachiligida immunitet reaktsiyasini keltirib chiqaradi, bu esa aterogenezni yanada tezlashtiradi (17). T-hujayralari bilan bog'liq mediatorlar lezyon atrofida tolali psevdokapsula hosil bo'lishi bilan SMH larning migratsiyasini va mitozini rag'batlantiradi (17). Lipid bilan to'ldirilgan makrofaglar apoptozdan o'tadi, bu tolali qopqoq ostida nekrotik yadro hosil bo'lishiga olib keladi, bu esa yorilishga moyil bo'lib, halokatli trombozning shakllanishiga olib keladi (14).

Har xil turdagi blyashkalar natijasida yuzaga keladigan parodontal kasallik (shu jumladan gingivit) Qo'shma Shtatlardagi 30 yosh va undan katta yoshdagi kattalarning 47,2 foiziga ta'sir qiladi (1). 65 yoshdan keyin bu ko'rsatkich 70% gacha oshadi (4). Og'iz bo'shlig'ini parvarish qilish odatlaridan tashqari, parodontal kasallikka hissa qo'shadigan omillar orasida ijtimoiy-iqtisodiy holat, jins (erkak > ayol), ma'lumot, ovqatlanish va chekish kiradi (4,5). 2009 va 2010 yillardagi ma'lumotlarga ko'ra, og'ir parodontal kasallik butun dunyo bo'ylab kattalarning 11 foiziga ta'sir qiladi va oltinchi eng keng tarqalgan kasallik (ma'lum bir vaqtda holatlar soni) (5). Parodontal kasallik va YQTK (yangi holatlar ehtimoli) yoshga qarab ortadi (3,5).

Ko'pgina epidemiologik tadqiqotlar parodontit (gingivit bundan mustasno) va yurak-qon tomir kasalliklari (8-14) o'rtasidagi bog'liqlikni ko'rsatdi. 2012 yilda, parodontit va yurak-qon tomir kasalliklari o'rtasidagi bog'liqlikni qo'llab-quvvatlovchi 10 yildan ortiq epidemiologik dalillardan so'ng, Amerika yurak assotsiatsiyasi ikki kasallik o'rtasidagi bog'liqlikni tasdiqlovchi ilmiy bayonotni nashr etdi, ammo sabab-oqibat aloqasi yo'qligini ta'kidladi (15).

O'tgan o'n yilliklardagi adabiyotlardan jamlangan ma'lumotlar parodontitning ateroskleroz uchun mustaqil xavf omili sifatidagi rolini tasdiqlaydi.(18). Ba'zi parodontal patogenlar, xususan, gram-manfiy anaeroblar, subgingival bioplyonkada mavjudligi miokard infarkti xavfining oshishi bilan bog'liq; nazorat bilan solishtirganda T. forsythia va P. gingivalis bilan koeffitsientlar mos ravishda 2,52 dan 2,99 gacha bo'lgan (19). Parodontitning o'ziga xos xususiyati gramm-manfiy bakteriyalarning ko'payishi bo'lib, ular lipopolisaharid (LPS) kabi patogenlik mexanizmi orqali kuchli immunitet reaktsiyasini qo'zg'atish qobiliyati bilan tavsiflanadi.(20). Bundan tashqari, ushbu bakterial turlarning ba'zilari chuqurroq to'qimalarga kirib, qon aylanish tizimiga kirib, asl yashash joylaridan uzoqda tizimli immunitet reaktsiyasini qo'zg'atish qobiliyatiga ega (21). Bir nechta in vivo va in vitro tadqiqotlar surunkali yallig'lanish bilan bog'liq bo'lgan parodontal bakteriyalar epiteliya-mezenximal o'tish orqali epiteliya to'siqni funktsiyasini buzishi mumkinligini ko'rsatdi.(22-24).

Epiteliya-mezenximaga o'tish qutblilik, sitoskeletal oqsillar va yopishqoqlikning yo'qolishi bilan boshlangan, epiteliya fenotipini yo'qotish va mezenximaga o'xshash xususiyatlarni olish bilan yakunlanadigan hujayra hodisalarini o'z ichiga oladi.(25). Bu epiteliya qatlamining sinxronizatsiyasining yo'qolishiga va mikro yaralar shakllanishiga olib keladi; Shunday qilib, harakatchan parodontal patogenlar yoki virulent omillarning asosiy biriktiruvchi to'qima va ta'sirlangan qon tomirlariga kirishini osonlashtiradi. Boshqa tomondan, parodontal bakteriyalar mezonning immun javobidan qochish uchun mudofaa strategiyasining bir qismi sifatida mezbon hujayralarga hujum qilishi mumkin (26). Ushbu hujayra ichidagi lokalizatsiya nafaqat tananing mudofaa mexanizmlaridan himoya qiladi, balki mikroblarga qarshi vositalar ta'siridan boshpana ham beradi (26) . Hujayra ichida joylashgan P. gingivalis kabi periodontopatogenlar harakatsiz qoladi yoki hujayra mexanizmlarini modulyatsiya qilish orqali ko'payadi (27). Replikatsiyadan so'ng P. gingivalis boshqa hujayralarni yuqtirish yoki qon aylanish tizimiga kirish uchun endotsitik resirkulyatsiya yo'li orqali epiteliya hujayralarini tark etadi (28). P. gingivalisning endotelial hujayralarga kirib borishida bakterial yuk ortadi. Bundan tashqari, P. gingivalis gingival epiteliya va endotelial hujayralarga kirib borishi Fusobacterium nucleatum tomonidan kuchaytirilishi mumkin (30) va T. forsythia (31). P. gingivalis ko'pikli hujayralar paydo bo'lishiga yoki ularning hujayralar ichida turg'unligiga sabab bo'lishi va shu bilan ikkilamchi yallig'lanish holatini keltirib chiqarishi, bu esa endotelial disfunktsiyaga olib kelishi isbotlangan. Shuningdek, parodontal kasallik, xususan parodontit, IL-6, IL-8, TNF-a kabi aterosklerotik tomir kasalliklari bilan bog'liq bo'lgan turli sitokinlarning surunkali ko'tarilishiga olib keladigan tizimli yallig'lanish reaktsiyasini rag'batlantiradi. Ulardan ba'zilari C-reaktiv oqsil (CRO) va fibrinogen kabi qon plazmasidagi oqsillarning jigarda tez sintezini va sekretsiyasini kuchaytirishi mumkin.(36.37). Bundan tashqari, lipopolisakkaridlar kabi bakterial maysulotlar qon oqimiga kirib, kuchli immunitet reaktsiyasini keltirib chiqarishi mumkin. Ushbu yuqorida aytib o'tilgan omillar endotelial hujayralarga ta'sir qilish, lipid metabolizmini modulyatsiya qilish va oksidlovchi holatni oshirish orqali aterosklerozni boshlashi mumkin (38).

Bir qator tadqiqotlar parodontitni endotelial disfunktsiya bilan bog'lagan va bu assotsiatsiya parodontit, aterosklerotik yurak-qon tomir kasalliklari va endotelial disfunktsiyaning bir nechta umumiy biomarkerlari tomonidan qo'llab-quvvatlanadi.(47). Ushbu biomarkerlarning ushbu korrelyatsiyaning kuchini aniqlash potentsialiga qaramay, ular hali ham "oltin standart" diagnostika markerlari hisoblanmaydi (47). Parodontit boshlanganda, lipid profilining o'zgarishi bilan birga yallig'lanish sitokinlarining namoyon bo'lishi sezilarli darajada oshadi, bu tromboz shakllanishi va tromboembolik asoratlarning rivojlanishi va kuchayishiga yordam beradi (57). PB CRO, to'qima plazminogen faollashtiruvchisi (t-PA) va PZL xolesterin (C), TNF-a kabi endotelial disfunktsiya va dislipidemiya

uchun mas'ul bo'lgan biomarkerlarning faollashishi bilan sezilarli darajada bog'liqligi xabar qilingan.58). Bundan tashqari, parodontit boshqa yallig'lanish biomarkerlarining, jumladan fon Villebrand omili (vWF), fibrinogen va endotelial progenitor hujayralarning yuqori sarum darajasi bilan bog'liq.(58). Qizig'i shundaki, bu biomarkerlarning sarum darajasi parodontal terapiyadan keyin pasayadi (59, 60).

Tizimli tekshiruv PB, YQTK va endotelial disfunktsiyaga oid dalillarning kuchini aniqlash uchun umumiy biomarkerlar guruhining sarum darajasini o'rganib chiqdi. Natijalar tahlili shuni ko'rsatdiki, turli xil yallig'lanish belgilari, xususan, IL-6 va CRO ko'tarilgan. Ushbu tizimli tekshiruv natijalari shuni ko'rsatadiki, endotelial disfunktsiya parodontal kasallik va aterosklerotik yurak-qon tomir kasalliklari o'rtasidagi bog'liqlik bo'lishi mumkin.(61). Bundan tashqari, aterosklerotik YQTK yanada og'irroq parodontit bilan bog'liqligi aniqlandi va bu yuqori zardobdagi yuqori sezuvchanlik ()-CRO darajasi bilan qayd etilgan.(62). Parodontit bilan bog'liq yuqori va yuqori sezgir (ys) ys-CRO aterosklerotik lezyonning oldindan mavjud bo'lgan yallig'lanish faolligiga qo'shimcha bosim yaratadi; demak, ACVD xavfini yanada oshiradi (63). Yaqinda ma'lum bo'lishicha, parodontit IL-6, PTX3 va sTWEAK ning yuqori darajalari bilan bog'liq bo'lib, miya kichik tomir kasalliklari bilan og'rigan bemorlarda ACVD ning ushbu turiga ega bo'lish ehtimoli deyarli 3 baravar oshiradi (64). Bu kalamushlarga P. gingivalis dan LPS kiritilgandan so'ng tizimli qon aylanishida qon tomir yallig'lanish biomarkerlari, IL-6, PTX3 va sTWEAKdagi o'zgarishlarni ko'rsatadigan in vivo tadqiqot natijalari bilan tasdiqlandi (65).

Darhaqiqat, hozirgi adabiyotlar PK va ACVD uchun umumiy biomarkerlar haqida qimmatli ma'lumotlarni taqdim etdi, bu erta salbiy yurak va qon tomir hodisalari xavfini sezilarli darajada kamaytirish uchun prognostik va diagnostik salohiyatni taklif qilishi mumkin. Biroq, bu borada qo'shimcha tadqiqotlar talab etiladi, chunki ACVD va PK biomarkerlaridan tashqari aniq belgilar hali to'liq aniqlanmagan (66,67).

2012 yilda Yevropa Parodontologiya Federatsiyasi (EFP) va Amerika Parodontologiya Akademiyasi (AAP) qo'shma seminarida PK va ACVDo'rtasidagi bog'liqlik haqida dalillar taqdim etildi.(45). Dalillar orasida periodontopatogen bakteriyalarning ACVDdagi roli va ikkala kasallik o'rtasidagi bog'liqlikni qo'llab-quvvatlovchi klinik (epidemiologik va interventsion) tadqiqotlar mavjud.(46).Klinik jihatdan ateroskleroznin qo'zg'atuvchilarini topish juda qiyin. Birinchidan, endotelial shikastlanish odatda asemptomatik tarzda rivojlanadi va rivojlanadi, bu esa potentsial qo'zg'atuvchini niqoblaydi. Ikkinchidan, bir nechta omillar umumiy yallig'lanish reaktsiyasiga olib kelishi mumkin, masalan, aterosklerotik o'zgarishlar va bu omillar birgalikda mavjud bo'lib, qo'zg'atuvchi omilni aniqlashni yanada murakkablashtiradi. Bundan tashqari, bu borada amalga oshirilgan aralashuvlar bo'yicha tadqiqotlar o'zgarmasligi, parodontal davolanishdan keyin simptomlarning vaqtincha yomonlashishi yoki simptomlarning yaxshilanishi kabi aralash natijalar haqida xabar berdi (65,67). Parodontal terapiyaning (PT) asosiy maqsadi patogen bakteriyalar sonini kamaytirish va shu bilan progressiv yallig'lanish va parodontitning qaytalanish ehtimolini kamaytirishdir (16). Roca-Millan va boshqalar tomonidan 10 ta klinik tadqiqotlarni tizimli ko'rib chiqish va meta-tahlil. parodontit terapiyasining yurak-qon tomir kasalliklari xavfiga ta'sirini umumlashtirdi. Terapiya natijasida quyidagilar ko'rsatildi: CRO, o'sma nekrozi faktor-a, interleykin-6 va leykotsitlar darajasining pasayishi. Terapiyadan keyin fibrinogen darajasi ham sezilarli darajada yaxshilandi. Bundan tashqari, parodontitni davolashdan keyin past zichlikdagi lipoproteinlar (PZL) darajasining sezilarli darajada pasayishi va yuqori zichlikdagi lipoproteinlarning (YZL) ko'payishi kuzatildi. Meta-tahlil shuni ko'rsatdiki, parodontitni jarrohliksiz davolash, umuman davolashdan farqli o'laroq, CRO ning sezilarli darajada pasayishiga olib keladi.

ASYQTK ni davolash va oldini olish uchun ishlatiladigan turli dorilar orasida statinlar parodontal kasalliklarni davolashda terapevtik salohiyatni ko'rsatdi (47,48). Statinlar 3 gidroksimetil glutaril koenzim A reduktaza (GMG-KoA reduktaza) inhibitörleridir. Ushbu dorilar turli xil halqa tuzilmalariga ega va AYQTK ning oldini olish uchun qonda PZL va xolesterin darajasini pasaytirishi ma'lum (49,50). Lipidlarni kamaytiradigan asosiy ta'sirga qo'shimcha ravishda, statinlar yallig'lanishga qarshi, antioksidant, antibakterial va immunoregulyatsion funktsiyalarni o'z ichiga olgan bir qator pleiotrop ta'sirga ega.(51,52).

Statinlarning yallig'lanishga qarshi ta'siri ularning yallig'lanishga qarshi sitokinlarni ingibatsiya qilish va yallig'lanishga qarshi faolligini oshirish qobiliyatiga bog'liq. Bu ta'sir birinchi navbatda hujayradan tashqari signal bilan boshqariladigan protein kinazlar (ERK), mitogen bilan faollashtirilgan protein kinaz (MAPK), protein kinaz signalizatsiya yo'li (PI3-Akt) faollashishi bilan bog'liq. Bundan tashqari, statinlar bakterial hujumga xo'jayini javobini modulyatsiya qilishga qodir; Shunday qilib, yallig'lanish vositasida suyak rezorbsiyasini oldini oladi va yangi suyak shakllanishini rag'batlantiradi (53). Hayvonlarning eksperimental modellaridan foydalangan holda statinlarni topikal qo'llash ularning metalloproteinazalarga ingibitiv ta'siridan tashqari, yallig'lanishga qarshi, mikroblarga qarshi va suyaklarni qayta qurish xususiyatlari natijasida alveolyar suyak rezorbsiyasining oldini olishga yordam berdi.(54).

5 yillik, populyatsiyaga asoslangan, raqobatbardosh kuzatuv tadqiqoti tizimli ravishda qo'llaniladigan statinlarni qabul qilmagan ishtirokchilarga nisbatan tishlarni yo'qotish tezligiga ta'sirini o'rganib chiqildi. Tadqiqot shuni ko'rsatdiki, statinlar bilan davolangan bemorlarda tishlarning yo'qolishi nazorat bilan solishtirganda kamaygan.(55). Bundan tashqari, parodontitning klinik belgilarining sezilarli yaxshilanishi ACVD ning preklinik kursini uzaytirishga va yurak xuruji, insult va trombozning o'limga olib keladigan oqibatlarini oldini olishga olib keladi. PK va ACVD o'rtasidagi munosabatlarni, ayniqsa qon tomir endoteliyasiga ta'sir qilish orqali aterogen kaskadga PK ning biologik ta'siri nuqtai nazaridan qo'shimcha aralashuvni o'rganish kerak. Umuman olganda, murakkab standart davolashda statinlarning parodontit to'qimasiga ta'siri, ayniqsa uni topikal qo'llash bo'yicha keyingi tadqiqotlarga ehtiyoj paydo bo'lishi shubhasiz. Statinlarning istiqbolli natijalariga qaramay, ularning yumshoq va qattiq to'qimalarni davolashning turli jihatlariga ta'siri, ayniqsa, yaralarni davolash va regeneratsiya bilan bog'liq holda qo'shimcha o'rganishni talab qiladi.

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