DIABETIK NEFROPATIYA PATOGENEZIDA RUX (Zn^{2+}) DISBALANSI NATIJASIDA KELIB CHIQADIGAN MORFOLOGIK O‘ZGARISHLAR

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Annotatsiya. *Mazkur maqolada diabetik nefropatiya (DN) patogenezida rux (Zn^{2+}) disbalansi va uning buyrak to‘qimasidagi morfologik o‘zgarishlar bilan bog‘liqligi tahlil qilingan. Surunkali giperglikemiya chaqirgan gipertsinkuriya va ZnT/ZIP transport oqsillari disfunksiyasi nefron hujayralarida rux tanqisligini keltirib chiqaradi. Bu holat SOD1 va Nrf2/metallotionein antioksidant tizimini susaytirib, podotsit oyoqchalari yassilanishi, bazal membrana qalinlashishi (>395–430 nm), Kimmelstil-Uilson tugunlari va tubulointerstitsial fibrozni tezlashtiradi.*

Kalit so‘zlar: *diabetik nefropatiya, rux disbalansi, podotsit, bazal membrana, mezangial ekspansiya, tubulointerstitsial fibroz*

Аннотация. *В статье анализируется взаимосвязь между дисбалансом цинка (Zn^{2+}) и морфологической перестройкой почек при диабетической нефропатии (ДН). Индуцированная гипергликемией гиперцинкурия и дисфункция транспортёров ZnT/ZIP вызывают дефицит цинка в нефронах, подавляя активность SOD1 и оси Nrf2/металлотионеин. Морфологически это проявляется сглаживанием ножек подоцитов, утолщением базальной мембраны (>395–430 нм), узелками Киммельстила–Уилсона и тубулоинтерстициальным фиброзом.*

Ключевые слова: *диабетическая нефропатия, дисбаланс цинка, подоциты, базальная мембрана, мезангиальная экспансия, тубулоинтерстициальный фиброз*

Annotation. *This article examines the relationship between zinc (Zn^{2+}) dyshomeostasis and renal morphological remodeling in diabetic nephropathy (DN). Hyperglycemia-induced hyperzincuria and altered ZnT/ZIP transporter expression cause intracellular zinc depletion, impairing SOD1 and the Nrf2/metallothionein antioxidant axis. Morphologically, this leads to podocyte foot process effacement, glomerular basement membrane thickening (>395–430 nm), Kimmelstiel–Wilson nodules, and tubulointerstitial fibrosis.*

Keywords: *diabetic nephropathy, zinc dyshomeostasis, podocyte effacement, glomerular basement membrane, mesangial expansion, tubulointerstitial fibrosis*

Kirish. Diabetik nefropatiya (DN) 1- va 2-tur qandli diabet bilan og‘rigan bemorlarning 30–40 foizida rivojlanib, terminal bosqichdagi surunkali buyrak yetishmovchiligining (SBY) eng asosiy sababi hisoblanadi [1, 2]. An’anaviy patogenetik yondashuvda asosiy e’tibor koptokcha ichi gipertenziyasi, renin-angiotenzin-aldosteron tizimi (RAAT) faollashuvi va glikozillanishning yakuniy mahsulotlari (AGEs) to‘planishiga qaratilsa-da, standart davolash choralari ko‘p hollarda nefronlarning strukturaviy yemirilishini to‘xtata olmaydi [1, 3]. So‘nggi yillardagi tadqiqotlar buyrak to‘qimasi butunligini saqlashda rux (Zn^{2+}) gomeostazi hal qiluvchi o‘rin tutishini ko‘rsatmoqda. Rux 300 dan ortiq fermentlar va 2000 dan ziyod transkripsiya omillari faolligini ta’minlab, koptokcha filtratsiya to‘sig‘i (KFT), podotsitlar sitoskeleti hamda proksimal kanalchalar epiteliysining antioksidant himoyasini boshqaradi [2, 4]. Qandli diabetda qon zardobida rux kamayishi (gipotsinkemiya) va siydik bilan ko‘p yo‘qotilishi (gipertsinkuriya) kuzatilib, bu holat albuminuriya darajasi hamda buyrak biopsiyasidagi morfologik o‘zgarishlar og‘irligi bilan to‘g‘ridan-to‘g‘ri bog‘liqdir [1, 6]. Ushbu maqolaning maqsadi — diabetik nefropatiya patogenezida rux disbalansi natijasida koptokcha va tubulointerstitsial qismda yuzaga keladigan morfologik o‘zgarishlarni zamonaviy ilmiy manbalar asosida tahlil qilishdan iborat.

ASOSIY QISM

Me’yorda koptokchalardan filtrlangan ruxning 90–95 foizi proksimal egri-bugri kanalchalar va Genle qovuzlog‘ida qayta so‘riladi. Hujayra ichiga Zn^{2+} kirishini ZIP (SLC39A1–14) oqsillari, hujayradan chiqishi va organellalarga taqsimlanishini esa ZnT (SLC30A1–10) transportyorlari boshqaradi [4]. Qandli diabetda surunkali giperglikemiya chaqirgan osmotik diurez va proteinuriya tufayli rux reabsorbsiyasi buziladi, shuningdek, kanalchalarda himoyalovchi ZnT1 oqsili kamayib, ZIP8 va ZIP14 muvozanati izdan chiqadi [1, 7]. Natijada podotsitlar, mezangiotsitlar va kanalcha epiteliysida hujayra ichi rux tanqisligi rivojlanadi. Hujayrada Zn^{2+} kamayishi uchta asosiy molekulyar mexanizm orqali morfologik shikastlanishni ishga tushiradi. Birinchidan, ruxga bog‘liq Cu/Zn-superoksiddismutaza (SOD1) fermenti faolsizlanadi va NOX4 fermenti hosil qilgan superoksid radikallari ($O_2^{\bullet -}$) hamda peroksinitrit ($ONOO^-$) hujayra membranalarini yemiradi [6, 8]. Ikkinchidan, B. Li [9] va H. Wu [8] ko‘rsatganidek, rux yetishmovchiligida Akt kinaza faolligi pasayib, Fyn kinaza hujayra yadrosiga kiradi va asosiy antioksidant omil — Nrf2 ni yadrodan chiqarib yuboradi; oqibatda metallotioneinlar (MT-1/2) va gemoksigenaza-1 (HO-1) sintezi to‘xtaydi.

Uchinchidan, rux tanqisligi mitoxondrial nafas olishni buzib, NADH/NAD^+ nisbatini oshiradi, lokal laktat-atsidoz va gipoksiya omili (HIF-1α) giperfaollashuvini keltirib chiqaradi [1, 2].

Buyrak patologiyasi jamiyati (RPS) xalqaro tasnifiga ko‘ra, DN da koptokcha o‘zgarishlari 4 ta sinfga (I — bazal membrana qalinlashishi; IIa/IIb — mezangial ekspansiya; III — Kimmelstil-Uilson tugunlari; IV — global glomerulosklerоz) bo‘linadi [10]. Z. Huang va hammualliflar (2025) aniqlashicha, rux tanqisligi dastlab podotsitlarda Wnt3a/β-katenin yo‘lini faollashtirib, tirqishli diafragma va sitoskeletning tayanch oqsillari — nefrin, podokaliksin hamda WT1 ekspressiyasini keskin kamaytiradi [2]. Elektron mikroskopiyada (TEM) podotsit oyoqchalarining (pedikulalarning) diffuz yassilanishi (foot process effacement), tirqishli diafragma yo‘qolishi va podotsitlarning bazal membranadan ko‘chishi kuzatiladi [2]. Shu bilan birga, ruxga bog‘liq matriks metalloproteinazalari (MMP-2, MMP-9) va TIMP-1 muvozanati buzilishi hamda IV tip kollagen ortiqcha sintezlanishi natijasida glomerulyar bazal membrana (GBM) diffuz qalinlashadi (RPS I sinf: ayollarda >395 nm, erkaklarda >430 nm) [2, 10]. Keyingi bosqichlarda (RPS II–III sinflar) TGF-β1 va CTGF ta’sirida mezangial matriks kengayishi (>25%) yuz berib, PAS va Masson trixrom bo‘yoqlarida hujayrasiz sklerotik Kimmelstil-Uilson tugunlari hamda arteriolalar gialinozi aniqlanadi [6, 10]. 2025–2026-yillardagi tadqiqotlar shuni ko‘rsatdiki, rux yetishmovchiligi proksimal kanalchalarda mitoxondrial laktat-atsidoz chaqiradi hamda GPX4 va FTH1 oqsillarini kamaytirib, epiteliy hujayralarining ferroptoz va apoptoz (kaspaza-3 orqali) yo‘li bilan nobud bo‘lishiga olib keladi [2, 5]. Morfologik jihatdan kanalchalarda apikal jiyakdor hoshiya (brush border) yo‘qolishi, gidropik distrofiya, kanalcha bazal membranasi (TBM) qalinlashishi va kanalchalar atrofiyasi (IFTA) kuzatiladi [5, 10]. Interstitsiyda esa TGF-β1/Smad3 va HIF-1α faollashib, fibroblastlar α-SMA-musbat miofibroblastlarga aylanadi hamda I, III tip kollagen va fibronektin to‘planib, tubulointerstitsial fibroz shakllanadi (1-jadval) [2, 5].

1-jadval

Diabetik nefropatiyada rux (Zn^{2+}) disbalansi chaqiradigan asosiy morfologik o‘zgarishlar

Nefron qismi (RPS sinfi)	**Molekulyar mexanizm**	**Morfologik (gistologik va TEM) o‘zgarishlar**	**Biomarker va bo‘yalish**
Podotsitlar (I–II sinf)	Wnt3a/β-katenin faollashuvi, SOD1 va MT-1/2 pasayishi [2, 8]	Pedikulalarning diffuz yassilanishi, tirqishli diafragma yo‘qolishi, podotsit ko‘chishi	↓ Nefrin, ↓ Podokaliksin, ↓ WT1; ↑ β-katenin

Bazal membrana — GBM (I sinf)	MMP-2/9 va TIMP-1 disbalansi, IV tip kollagen ortishi [2, 10]	GBM diffuz qalinlashishi (ayollarda >395 nm, erkaklarda >430 nm), qatlamlanish	↑ IV tip kollagen, ↑ Laminin; PAS (+)
Mezangiy (II–III sinf)	Nrf2 bloklanishi, TGF-β1 va CTGF ortishi [6, 9]	Mezangial matriks kengayishi (>25%), Kimmelstil-Uilson tugunlari, arteriolalar gialinozi	↑ TGF-β1, ↑ CTGF; PAS (+) va Masson (+) tugunlar
Kanalchalar va interstitsiy (IFTA)	Laktat-atsidoz, ↓ GPX4 (ferroptoz), HIF-1α va EMT [2, 5]	Jiyakdor hoshiya yo‘qolishi, vakuolyar distrofiya, kanalcha atrofiyasi, interstitsial fibroz	↓ GPX4, ↑ α-SMA, ↑ I/III tip kollagen, ↑ FN1

Xulosa qilib aytganda, rux (Zn^{2+}) disbalansi diabetik nefropatiyada koptokcha va kanalchalar shikastlanishini tezlashtiruvchi muhim patogenetik omildir. Hujayra ichi rux tanqisligi SOD1 va Nrf2/metallotionein himoyasini izdan chiqarib, podotsitopatiya, GBM qalinlashishi, Kimmelstil-Uilson tugunlari, kanalchalar ferroptozi hamda tubulointerstitsial fibrozga olib keladi. G. Ozkan va hammualliflar (2026) ta’kidlaganidek, kechki bosqichda berilgan rux molekulyar ko‘rsatkichlarni yaxshilasa-da, shakllangan chuqur sklerozni to‘liq qaytara olmaydi [5]. Shu bois qandli diabetning erta bosqichlarida (RPS I–IIa sinflar) rux tanqisligini aniqlash va fiziologik dozalarda korreksiyalash nefronlarning morfologik butunligini saqlab qolishda muhim amaliy ahamiyatga ega.

Foydalanilgan adabiyotlar

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