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DIABETIK TO‘PIQ SINDROMIDA IMMUNO-METABOLIK DISBALANS VA TO‘QIMA REGENERATSIYASINING SUSAYISHI

Ruzimurodov N.F., Raxmonov N.N., Azizova Z.Sh., Xosilbekova D.M., Abdualieva M.B.
O’zR FA Immunologiya va inson genomikasi instituti

РЕЗЮМЕ

Актуальность. *Сахарный диабет 2-го типа (СД2) часто осложняется синдромом диабетической стопы (СДС), при котором хроническая гипоксия и воспаление приводят к эндотелиальной дисфункции, угнетению ангиогенеза и замедлению заживления ран. Оценка ключевых ростовых факторов может уточнить патогенез и улучшить раннюю стратификацию риска.*

Цель исследования. *Оценить изменения сывороточных уровней VEGF-A, IGF-1 и TGF-β1 у пациентов с СД2 и СДС по сравнению со здоровыми лицами.*

Материал и методы. *Обследованы 84 участника 50-65 лет: контроль (n=26), СД2 без осложнений (n=30) и СД2+СДС (n=28). Концентрации VEGF-A, IGF-1 и TGF-β1 определяли методом ИФА (ELISA) с использованием сертифицированных тест-систем. Статистический анализ выполнен в Statistica 6.0; различия считались значимыми при p<0,05.*

Результаты. *У пациентов с СД2 выявлено достоверное снижение VEGF-A и IGF-1 по сравнению с контролем (p<0,001). При сочетании СД2 и СДС снижение VEGF-A и IGF-1 было более выраженным и сопровождалось нарастанием дефицита репаративных медиаторов; выявленный профиль соответствует подавлению ангиогенной активности, нарушению микроциркуляции и снижению регенераторного потенциала тканей.*

Ключевые слова: *ангиогенез, гипоксия, воспаление, регенерация, фиброз, сосудистая дисфункция, цитокины, эндотелий.*

SUMMARY

Background. *Type 2 diabetes mellitus (T2DM) is frequently complicated by diabetic foot syndrome (DFS), where chronic hypoxia and inflammation lead to endothelial dysfunction, suppression of angiogenesis, and delayed wound healing. Assessment of key growth factors may clarify the pathogenesis and improve early risk stratification.*

Objective. *To assess changes in serum levels of VEGF-A, IGF-1 and TGF-β1 in patients with T2DM and DFS compared with healthy individuals.*

Materials and methods. *Eighty-four participants aged 50–65 years were enrolled: controls (n=26), uncomplicated T2DM (n=30) and T2DM+DFS (n=28). Serum VEGF-A, IGF-1 and TGF-β1 were measured by certified ELISA kits. Statistical analysis was performed using Statistica 6.0; p<0.05 was considered significant.*

Results. *Patients with T2DM demonstrated a significant decrease in VEGF-A and IGF-1 levels compared with controls(p<0.001). In T2DM combined with DFS, the decline in angiogenic and reparative mediators was more pronounced, consistent with suppressed angiogenic activity, microcirculatory impairment and reduced tissue regenerative capacity.*

Keywords: *angiogenesis, hypoxia, inflammation, regeneration, fibrosis, vascular dysfunction, cytokines, endothelium.*

2-tur qandli diabet (2-tur QD) jahon miqyosda kasallanish va o‘lim ko‘rsatkichlarining muhim omillaridan biri bo‘lib qolmoqda. So‘nggi o‘n yilliklarda diabet tarqalishi tez sur’atlar bilan ortib, ayniqsa daromadi past va o‘rta bo‘lgan mamlakatlarda yuklama keskin oshdi [20].

2-tur QD asoratlari ko‘p omilli bo‘lib, mikro- va makrotomir shikastlanishlarini o‘z ichiga oladi. Ulardan eng og‘ir va iqtisodiy jihatdan katta xarajat talab qiladigani diabetik to‘piq sindromi (DTS) hisoblanadi. DTS fonida oyoq panjasi sohasida ishemiya, neyropatiya va infeksiya bir-birini kuchaytirib, surunkali, qiyin bituvchi yara jarayoniga olib keladi [7,9].

DTS patogenezida surunkali past-intensiv yallig‘lanish, immuno-metabolik disregulyatsiya va endoteliy disfunksiyasi yetakchi o‘rin tutadi. Adipokinlar va sitokinlar muvozanatining buzilishi insulinrezistentlik va tomir asoratlari bilan bog‘liqligi haqida dalillar mavjud [1,3].

Shu bilan birga, DTSda yallig‘lanish mediatorlari va o‘sish omillarining integratsiyalashgan profili klinik kogortalarda yetarlicha aniqlanmagan. Ko‘plab ishlar

alohida bo‘g‘inlarga (faqat interleykinlar yoki faqat MMP va h.k.) e’tibor qaratadi, bu esa “sitokin faollashuvi → angiogenez → matriks remodellashtirilishi → reparatsiya” uzluksiz patogenetik o‘qini to‘liq baholashni cheklaydi [11,12]. Shuning uchun DTSda VEGF-A, IGF-1 va TGF-β1 kabi kalit omillarni birgalikda baholash dolzarbdir.

TADQIQOT MAQSADI

Sog‘lom shaxslar ko‘rsatkichlari bilan solishtirganda 2-tur QD va DTS bo‘lgan bemorlarda VEGF-A, IGF-1 hamda TGF-β1 o‘sish omillarining zardob darajalaridagi o‘zgarishlarni baholash.

MATERIALLAR VA USULLAR

Tadqiqotda 50–65 yoshdagi 58 nafar (ayol va erkak) 2-tur QD tashxisi qo‘yilgan bemorlar ishtirok etdi. Ular ikki guruhga ajratildi: 1) asoratsiz 2-tur QD guruhi (n=30); 2) 2-tur QD fonida rivojlangan DTS guruhi (n=28). Nazorat guruhini yoshi va jinsi bo‘yicha mos 26 nafar amalda sog‘lom shaxslar tashkil etdi.

Tadqiqotga klinik va laborator jihatdan tasdiqlangan 2-tur QD tashxisi bo‘lgan, kasallik muddati 5 yildan oshmagan, uglevod almashinuvi kompensatsiya yoki subkompensatsiya bosqichidagi shaxslar kiritildi. Barcha ishtirokchilar yozma ravishda xabardor rozilik berdi.

1-tur diabet, o‘tkir yallig‘lanish yoki infeksion jarayonlar, surunkali buyrakva/yoki jigar yetishmovchiligi, yomon sifatli o‘smalar, autoimmun kasalliklar va tizimli vaskulitlar mavjud shaxslar, shuningdek, so‘nggi 3 oyda immunomodulyatorlar, GKS yoki sitostatiklarni qabul qilganlar tadqiqotdan chiqarib tashlandi.

Barcha bemorlarda klinik, laborator va instrumental tekshiruvlar amalga oshirildi: antropometriya (bo‘y, vazn, tana vazni indeksi (TVI)), arterial bosim, uglevod almashinuvi (och qoringa glyukoza, glikirlangan gemoglobin (HbA1c)), lipid profili va insulinrezistentlik indeksi (HOMA-IR). Pastki oyoq tomirlarini baholash uchun UTT, dopplerografiya hamda klinik ko‘rsatma bo‘lsa angiografiya bajarildi.

Immunologik tekshiruvlar Immunologiya va inson genomikasi instituti bazasida o‘tkazildi. Biologik material sifatida och qoringa olingan venoz qon zardobi ishlatildi. VEGF-A, IGF-1 va TGF-β1 konsentratsiyalari sertifikatlangan immune-ferment tahlil (IFT) test-tizimlari («Vektor-Best», «BioHimMak», Rossiya) yordamida ishlab chiqaruvchi yo‘riqnomalariga muvofiq aniqlandi.

Statistik tahlil Statistica 6.0 (StatSoft Inc., AQSh) dasturida bajarildi. Miqdoriy ko‘rsatkichlar uchun o‘rtacha qiymat (M) va standart xatolik (m) hisoblandi; guruhlararo taqqoslash Student t-test yordamida amalga oshirildi. Shuningdek, mediana (Me), interkvartil oraliq [Q1–Q3] va 95% ishonch oralig‘i (95% IO) keltirildi. $p<0,05$ qiymatlar ahamiyatli deb qabul qilindi.

NATIJALAR VA MUHOKAMA

Bu tadqiqotda angiogenez va to‘qima rekonstruktsiyasi bilan bog‘liq muhim o‘sish omillari bo‘lgan VEGF-A, IGF-1 va TGF-β1ning plazma darajalarini nazorat guruhi (26 kishi), asoratsiz 2-tur qandli diabet (2-tur QD) guruhi (30 kishi) va 2-tur QD fonida diabetik to‘piq sindromi (DTS) mavjud bo‘lgan guruh (2-tur QD+DTS, 28 kishi)da tekshirildi (jadval). Ma’lumotlar o‘rtacha qiymati (M±m), median (Me), interkvartil diapazonu ([Q1; Q3]) va 95% IO yordamida keltirilgan; $p<0,05$ bo‘lgan farqlar muhim, $p<0,001$ bo‘lgan farqlar esa ancha yuqori darajada ishonchli hisoblangan.

Tekshirilgan guruhlarda o‘sish omillarining zardob darajalari

Ko‘rsatkich	M±m	Me [Q1; Q3]	95% IO	p
Nazorat guruhi, n=26				
VEGF-A, pg/ml	129,67±7,69	115,91 [102,89; 129,64]	113,83–145,51	—
IGF-1, pg/ml	88,63±3,13	94,68 [78,25; 101,42]	82,18–95,08	—
TGF-β1, pg/ml	41,19±2,28	40,84 [30,68; 49,99]	36,50–45,90	—
2-tur QD guruhi, n=30				
VEGF-A, pg/ml	97,21±4,37	97,44 [87,27; 122,87]	88,28–106,16	<0,001*
IGF-1, pg/ml	77,56±3,01	77,44 [67,72; 82,36]	71,39–83,74	<0,001*
TGF-β1, pg/ml	54,58±2,37	51,74 [44,56; 66,22]	49,72–59,44	<0,001*
2-tur QD + DTS guruhi, n=28				
VEGF-A, pg/ml	88,96±3,15	83,20 [77,37; 83,20]	82,49–95,43	<0,001*
IGF-1, pg/ml	64,64±2,71	66,85 [53,12; 72,42]	59,07–70,28	<0,001*
TGF-β1, pg/ml	66,57±2,55	69,13 [58,41; 76,39]	61,34–71,80	<0,001*

Izoh: * – nazorat guruhi bilan solishtirganda farqlar ishonchli. Me – median; Q1 – 25-persentil; Q3 – 75-persentil.

VEGF-A ko‘rsatkichi nazorat guruhida 129,67±7,69 pg/ml bo‘lib, mediana qiymati 115,91 pg/ml [102,89; 129,64] ni tashkil etdi. 95% IO 113,83–145,51 pg/ml oralig‘ida joylashgan. 2-tur QD guruhida VEGF-A darajasi nazorat guruhidan ancha pasayib, 97,21±4,37 pg/mlga tushib ketdi. Bu guruhning mediana qiymati 97,44 pg/ml [87,27; 122,87] bo‘lib, 95% IO 88,28–106,16 pg/ml oralig‘ida joylashgan. Statistik tekshiruv natijalarida VEGF-A o‘zgarishining nazorat guruhi bilan solishtirganda aniq va ishonchli farq borligini tasdiqladi ($p<0,001$).

2-tur QD+DTS guruhida VEGF-A ko‘rsatkichlari yanada past qiymatlarni namoyon etdi: 88,96±3,15 pg/ml (Me 83,20 pg/ml [77,37; 83,20]; 95% IO 82,49–95,43 pg/ml), bu ham nazoratga nisbatan $p<0,001$ darajada ishonchli farqni ko‘rsatdi. Amaliy jihatdan baholaganda, nazoratga nisbatan VEGF-A ning kamayishi 2-tur QD guruhida taxminan 25% atrofida, 2-tur QD+DTS guruhida esa 30% ga yaqin bo‘lib, DTS qo‘shilishi angiogen javobning susayishini kuchaytirishi mumkinligini ko‘rsatadi. VEGF-A ning pasayishi DTSning klinik patogeneziga xos bo‘lgan mikrotsirkulyatsiya yetishmovchiligi, endoteliy disfunksiyasi va surunkali ishemiya bilan mos keladi.

IGF-1 nazorat guruhida 88,63±3,13 pg/ml bo‘lib, median qiymat 94,68 pg/ml [78,25,101,42], 95% IO 82,18–95,08 pg/ml sifatida qayd etildi. 2-tur QD guruhida IGF-1 konsentratsiyasi nazoratga nisbatan pasayib, 77,56±3,01 pg/mlni tashkil etdi (Me 77,44 pg/ml [67,72; 82,36]; 95% IO 71,39–83,74 pg/ml). Ushbu pasayish ham statistik jihatdan ishonchli bo‘lib, $p<0,001$ ga teng.

2-tur QD+DTS guruhida IGF-1 darajasi eng past ko‘rsatkichlarga tushib, 64,64±2,71 pg/ml bo‘ldi (Me 66,85 pg/ml [53,12,72,42]; 95% IO 59,07–70,28 pg/ml), farq nazoratga nisbatan $p<0,001$ darajada ishonchli bo‘ldi. Nazorat bilan taqqoslanganda IGF-1 ning kamayishi 2-tur QD guruhida taxminan 12–13%, 2-tur QD+DTS guruhida esa 25–30% atrofida bo‘lib, DTS sharoitida reparativ-potensial (proliferatsiya, epitelizatsiya, fibroblast faolligi) bilan bog‘liq mexanizmlar sezilarli darajada cheklanayotganini ko‘rsatadi. IGF-1 ning pasayishi yaralarning kech bitishi, granulyatsiya to‘qimasi yetilishining sustligi va regeneratsiya resursining kamayishi bilan patogenetik bog‘liq bo‘lishi ehtimoli bor.

TGF-β1 nazorat guruhida 41,19±2,28 pg/ml bo‘lib, Me 40,84 pg/ml [30,68,49,99], 95% IO 36,50–45,90 pg/ml diapazonda qayd etildi. 2-tur QD guruhida TGF-β1 darajasi 54,58±2,37 pg/mlgacha oshdi (Me 51,74 pg/ml [44,56,66,22]; 95% IO 49,72–59,44 pg/ml) va nazoratga nisbatan farq $p<0,001$ darajada ishonchli bo‘ldi.

2-tur QD+DTS guruhida TGF-β1 yanada yuqori bo‘lib, 66,57±2,55 pg/mlni tashkil etdi (Me 69,13 pg/ml [58,41,76,39]; 95% IO 61,34–71,80 pg/ml), farq nazoratga nisbatan ham, klinik jihatdan ham e’tiborga molik darajada ($p<0,001$) bo‘lib qoldi. TGF-β1 ning oshishi diabet fonida to‘qima qayta tuzilishi (remodellashtirish) va fibrogen javobning kuchayishi, shuningdek surunkali yallig‘lanish fonida kollagen sintezi va matriks o‘zgarishlariga moyillik bilan izohlanishi mumkin. Ayniqsa DTS sharoitida yuqori TGF-β1 fonida VEGF-A va IGF-1 ning pasayishi “angiogenez/reparatsiya susayishi + remodellashtirish/fibroz yo‘nalishi” kabi noqulay biologik profil shakllanishiga ishora qiladi.

Olingan natijalar shuni ko‘rsatdiki, 2-tur QD ning o‘ziyoq angiogenez va reparatsiya bilan bog‘liq mediatorlar muvozanatini buzadi: VEGF-A va IGF-1 ishonchli kamayadi, TGF-β1 esa oshadi. DTS qo‘shilganda bu o‘zgarishlar yanada keskinlashib, VEGF-A va IGF-1 bo‘yicha pasayish chuqurlashadi, TGF-β1 esa yuqori darajada saqlanadi. Bunday kombinatsiya DTSning klinik patogenezida endoteliy disfunktsiyasi, mikrotsirkulyator yetishmovchilik, surunkali yara jarayonining cho‘zilishi hamda to‘qima reparatsiyasi samaradorligining pasayishini biokimyoviy jihatdan asoslab beradi.

Xulosa qilinganda, VEGF-A, IGF-1 va TGF-β1 ning birgalikdagi bahosi 2-tur QD va ayniqsa 2-tur QD+DTS holatlarida angiogenez–reparatsiya–remodellashtirish o‘qidagi disbalansni aks ettiradigan kompleks laborator profilni beradi va keyingi bosqichlarda klinik og‘irlik, yara bitish muddati hamda asoratlar xavfini prognoz qilish bilan bog‘liq tahlillar uchun asos bo‘lib xizmat qilishi mumkin.

ADABIYOTLAR

1. Abdalla M., Elhassan M., Osman S., et al. Serum leptin and adiponectin levels in patients with diabetic foot ulcers: correlation with insulin resistance and inflammation. //Frontiers in Endocrinology. 2023. Vol. 14. Article 1224031. DOI:10.3389/fendo.2023.1224031.
2. Border W. A., Noble N. A. Transforming growth factor beta in tissue fibrosis //New England Journal of Medicine. 1994. Vol. 331, No. 19. P. 1286–1292. DOI:10.1056/NEJM199411103311907.
3. Chen L., Zhang Y., Li Y., et al. Adipokine imbalance and vascular complications in type 2 diabetes: focus on the role of inflammation. //Metabolism: Clinical and Experimental. 2024. Vol. 155. P.155217. DOI:10.1016/j.metabol.2024.155217.
4. Gao F., Chen L., Li M., et al. Regulation of angiogenesis by VEGF-A signaling in diabetes and its complications // Journal of Molecular Endocrinology. 2021. Vol. 67, No. 2. P. 79–94. DOI:10.1530/JME-21-0032.
5. Gubbi S., Quipildor G. F., Barzilai N., et al. Growth hormone and IGF-1 in aging and diabetes // Molecular and Cellular Endocrinology. 2021. Vol. 519. P.111–130. DOI:10.1016/j.mce.2020.111130.
6. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. // Brussels: IDF, 2024. 152 p. ISBN 978-2-930229-91-8.
7. International Working Group on the Diabetic Foot (IWGDF). IWGDF Guidelines on the Prevention and Management of Diabetic Foot Disease. 2023.

URL: https://iwgdfguidelines.org/guidelines
8. Jiang Y., Wang C., Zhang J., et al. Mechanisms of TGF-β1 activation in chronic diabetic ulcers // Frontiers in Immunology. 2021. Vol. 12. Article 654210. DOI:10.3389/fimmu.2021.654210.
9. Kiliç Ü., Öztürk M., Gülmez A., et al. Global prevalence of diabetic foot ulcers: a systematic review and meta-analysis // Diabetes Research and Clinical Practice. 2025. Vol. 213. P. 111–119. DOI:10.1016/j.diabres.2025.111119.
10. Kim J., Park S., Kim J. H., et al. Reduced IGF-1 expression impairs keratinocyte migration and angiogenesis in diabetic wounds // Experimental Dermatology. 2020. Vol. 29, No. 11. P. 1064–1072. DOI:10.1111/exd.14166.
11. Qin X., Wang Y., Zhang S., et al. Dysregulation of VEGF and TGF-β pathways in diabetic foot ulcers: a mechanistic link to impaired wound healing // Wound Repair and Regeneration. 2025. Vol.33, No.2. P.142–153. DOI:10.1111/wrr.13125.
12. Sidhu G. S., Yadav R., Nanda S., et al. Role of matrix metalloproteinases and cytokine profile in chronic diabetic wounds: correlation with angiogenic markers // International Journal of Molecular Sciences. 2024. Vol. 25, No.4. Article 2398. DOI:10.3390/ijms25042398.
13. Tian L., Hou X., Wang L., Zhang Y. Hypoxia-induced regulation of VEGF-A expression and its role in diabetic wound healing // Frontiers in Endocrinology. 2022. Vol. 13. Article 927634. DOI:10.3389/fendo.2022.927634.
14. World Health Organization. Diabetes fact sheet. // Geneva: WHO, 2024. URL: https://www.who.int/news-room/fact-sheets/detail/diabetes (дата обращения: 24.10.2025).
15. Wu C., Li J., Gao X., et al. Transforming growth factor beta signaling in wound healing and fibrosis in diabetes // Journal of Translational Medicine. 2018. Vol. 16, No.1. P.1–12. DOI:10.1186/s12967-018-1583-0.
16. Wu Y., Sun Q., Chen G., et al. Circulating IGF-1 levels and metabolic outcomes in diabetes: a population-based study // Diabetes & Metabolism Journal. 2021. Vol. 45, No.4. P.560–570. DOI:10.4093/dmj.2020.0158.
17. Xue M., Jackson C. J., Campbell D., et al. Dysregulation of TGF-β1 signaling in chronic wounds of diabetic patients: implications for antifibrotic therapy // Cells. 2023. Vol.12, No. 2. Article 270. DOI:10.3390/cells12020270.
18. Yuen K. C. J., Dunger D. B., Cutfield W. S. IGF-1 physiology and clinical implications in diabetes and wound healing // Diabetes Care. 2022. Vol.45, No.7. P.1598–1609. DOI:10.2337/dci21-0043.
19. Zhang X., Zhang G., Zhang H., et al. Impaired HIF-1α and VEGF expression in diabetic wound healing: role of hyperglycemia and oxidative stress // International Journal of Molecular Medicine. 2019. Vol. 44, No. 2. P.423–433. DOI:10.3892/ijmm.2019.4217.
20. Zhou B., Afshin A., Bixby H., et al. Global trends in diabetes prevalence, diagnosis, and control from 1990 to 2022: a pooled analysis of 680 population-based studies with 27 million participants // The Lancet. 2024. Vol.403, No.10414. P.1123–1139. DOI:10.1016/S0140-6736(24)00123-5.
