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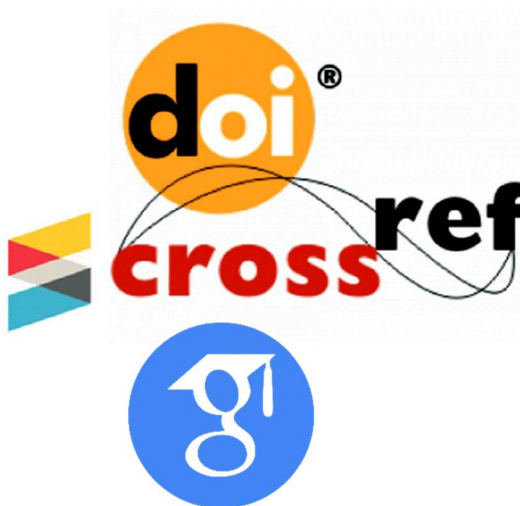
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ABSTRACT

Objective. To evaluate serum BMP-7 levels in patients with type 2 diabetes mellitus (T2DM) and to assess their associations with clinical and laboratory parameters according to chronic kidney disease (CKD) phenotypes defined by glomerular filtration rate (GFR) and albuminuria status. **Materials and Methods.** A total of 153 patients with T2DM were enrolled and classified into four phenotypic groups: NRF/NA (normal renal function/normoalbuminuria, n=35), DRF/NA (decreased renal function/normoalbuminuria, n=35), NRF/EA (normal renal function/elevated albuminuria, n=35), and DRF/EA (decreased renal function/elevated albuminuria, n=30). Eighteen healthy individuals served as controls. Serum BMP-7 levels were measured using enzyme-linked immunosorbent assay (ELISA). Outliers were excluded before analysis based on Tukey's method and physiological plausibility assessment. Group comparisons were performed using the Kruskal–Wallis test followed by Dunn's post-hoc analysis, with Benjamini–Hochberg false discovery rate (FDR) correction for multiple testing. Effect sizes (ε^2) were reported. Associations were evaluated using Spearman's correlation analysis. **Results.** After FDR correction, no statistically significant differences in BMP-7 levels were observed between the study groups ($q=0.092$). In the overall T2DM cohort (n=135), the only significant correlation of BMP-7 was found with C-peptide levels ($\rho=0.176$; $p=0.030$). No significant associations were observed with GFR, albuminuria, cystatin C, C-reactive protein (CRP), HbA1c, or proBNP ($p>0.05$). The highest BMP-7 concentrations were detected in the

NRF/EA (146 ± 35.9 pg/mL) and DRF/NA (145 ± 31.5 pg/mL) groups. **Conclusion.** In established CKD, serum BMP-7 is not a discriminative biomarker of renal phenotype in patients with T2DM. Its positive association with C-peptide suggests a potential role of BMP-7 in supporting pancreatic β -cell functional activity.

Keywords: BMP-7, bone morphogenetic protein-7, diabetic nephropathy, chronic kidney disease, type 2 diabetes mellitus, C-peptide, albuminuria, glomerular filtration rate.

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BMP-7 NING C-PEPTID BILAN BOG'LIQLIGI: 2-TIP QANDLI DIABETDA BETA-HUJAYRA REZERV MARKERI

ANNOTATSIYA

Maqsad. 2-tip qandli diabet (2-TQD) bilan og'rgan bemorlarda qon zardobidagi BMP-7 darajasini hamda uning klinik-laborator ko'rsatkichlar bilan bog'liqligini buyrak surunkali kasalligi (BSK) fenotipiga — koptokchali filtratsiya tezligi (KFT) va albuminuriya holatiga — qarab o'rganish.

Materiallar va usullar. Tadqiqotga 2-TQD bilan og'rgan 153 bemor kiritilib, ular to'rt fenotipga ajratildi: NRF/NA (normal KFT/normoalbuminuriya, $n=35$), DRF/NA (pasaygan KFT/normoalbuminuriya, $n=35$), NRF/EA (normal KFT/oshgan albuminuriya, $n=35$), DRF/EA (pasaygan KFT/oshgan albuminuriya, $n=30$); 18 sog'lom shaxs nazorat guruhini tashkil etdi. BMP-7 IFA usulida aniqlandi. Cheklamalar (outlierlar) Tukey usuli va fiziologik ishonchlik asosida tahlildan oldin chiqarib tashlandi. Guruhlararo taqqoslashlar Kruskal–Uollis mezonini va Dann post-hoc tahlili bilan o'tkazildi; ko'p taqqoslashlar Benjamini–Xoxberg FDR usuli bilan to'g'rilandi. Effekt o'lchamlari (ε^2) keltirildi. Bog'liqliklar Spirman korrelyatsiyasi orqali baholandi.

Natijalar. FDR to'g'rilashdan so'ng guruhlar o'rtasida BMP-7 darajasi bo'yicha statistik ahamiyatli farqlar aniqlanmadi ($q=0,092$). Umumiy 2-TQD kogortasida ($n=135$) BMP-7 ning yagona ahamiyatli korrelyatsiyasi C-peptid bilan kuzatildi ($\rho=0,176$; $p=0,030$). KFT, albuminuriya, sistatin C, CRP, HbA1c va proBNP bilan bog'liqliklar ahamiyatsiz edi ($p>0,05$). BMP-7 ning eng yuqori qiymatlari NRF/EA ($146 \pm 35,9$ pg/ml) va DRF/NA ($145 \pm 31,5$ pg/ml) guruhlarida qayd etildi.

Xulosa. Shakllangan BSK sharoitida qon zardobidagi BMP-7 2-TQD da buyrak fenotipining diskriminativ markeri hisoblanmaydi. Uning C-peptid bilan ijobiy bog'liqligi BMP-7 ning oshqozon osti bezi beta-hujayralari funksional faolligini qo'llab-quvvatlashdagi mumkin bo'lgan rolini ko'rsatadi.

Kalit so'zlar: BMP-7; suyak morfogenetik oqsili-7; diabetik nefropatiya; buyrak surunkali kasalligi; 2-tip qandli diabet; C-peptid; albuminuriya; koptokchali filtratsiya tezligi.

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СВЯЗЬ BMP-7 С УРОВНЕМ С-ПЕПТИДА: МАРКЕР РЕЗЕРВА β -КЛЕТОК ПРИ САХАРНОМ ДИАБЕТЕ 2 ТИПА

АННОТАЦИЯ

Цель. Изучить уровень BMP-7 в сыворотке крови у пациентов с сахарным диабетом 2 типа (СД2) и его взаимосвязь с клинико-лабораторными показателями в зависимости от фенотипа хронической болезни почек (ХБП), определяемого по скорости клубочковой фильтрации (СКФ) и уровню альбуминурии.

Материалы и методы. В исследование были включены 153 пациента с СД2, распределённые на четыре фенотипические группы: NRF/NA (нормальная СКФ/нормоальбуминурия, $n=35$), DRF/NA (сниженная СКФ/нормоальбуминурия, $n=35$), NRF/EA (нормальная СКФ/повышенная альбуминурия, $n=35$), DRF/EA (сниженная СКФ/повышенная альбуминурия, $n=30$); контрольную группу составили 18 здоровых лиц. Уровень BMP-7 определяли методом иммуноферментного анализа (ИФА). Выбросы исключались до проведения анализа на основании метода Тьюки и оценки физиологической достоверности. Межгрупповые сравнения выполняли с использованием критерия Краскела–Уоллиса и post-hoc анализа Данна; множественные сравнения корректировали методом Benjamini–Hochberg FDR. Были рассчитаны размеры эффекта (ε^2). Корреляционные связи оценивали с помощью коэффициента Спирмена.

Результаты. После FDR-коррекции статистически значимых различий уровня BMP-7 между группами не выявлено ($q=0,092$). В общей когорте пациентов с СД2 ($n=135$) единственная значимая корреляция BMP-7 была обнаружена с уровнем С-пептида ($\rho=0,176$; $p=0,030$). Связи с СКФ, альбуминурией, цистатином С, С-реактивным белком (CRP), HbA1c и proBNP были статистически незначимыми ($p>0,05$). Наиболее высокие значения BMP-7 зарегистрированы в группах NRF/EA ($146\pm 35,9$ пг/мл) и DRF/NA ($145\pm 31,5$ пг/мл).

Заключение. В условиях сформировавшейся ХБП уровень BMP-7 в сыворотке крови не является дискриминативным маркером почечного фенотипа при СД2. Положительная корреляция с уровнем С-пептида указывает на возможную роль BMP-7 в поддержании функциональной активности β -клеток поджелудочной железы.

Ключевые слова: BMP-7, костный морфогенетический белок-7, диабетическая нефропатия, хроническая болезнь почек, сахарный диабет 2 типа, С-пептид, альбуминурия, скорость клубочковой фильтрации.

Kirish

Suyak morfogenetik oqsili-7 (BMP-7, bone morphogenetic protein-7) — TGF- β oqsillari oilasiga mansub bo'lib, buyrak to'qimasida ko'plab boshqaruvchi vazifalarni bajaradigan plejotrop sitokin hisoblanadi. Normal sharoitda BMP-7 asosan distal kanalcha hujayralari va yig'uvchi naychalar tomonidan ishlab chiqariladi va antifibrotik, antiapoptotik hamda yallig'lanishga qarshi ta'sir ko'rsatadi [1]. Diabetik nefropatiyaning eksperimental modellarida tubulointerstitsial fibroz va glomeruloskleroz kuchayishi bilan birga to'qima va zardobdagi BMP-7 konsentratsiyasining progressiv pasayishi kuzatiladi [2, 3].

Klinik tadqiqotlarda 2-TQD bilan bog'liq BSK da qon zardobidagi BMP-7 ning diagnostik va prognostik qiymati haqidagi ma'lumotlar qarama-qarshidir. Ayrim mualliflar nefropatiya progressiyasida uning konsentratsiyasi pasayishini ko'rsatsa [4], boshqalari turli darajadagi buyrak disfunktsiyasiga ega guruhlar o'rtasida ahamiyatli farqlar topmaydi [5]. Bunday tafovutlar o'rganilayotgan kogortalarning buyrak fenotipi bo'yicha bir xil emasligi bilan bog'liq bo'lishi

mumkin, chunki ko'pchilik tadqiqotlar pasaygan KFT va albuminuriya mavjudligi bo'yicha differentsiatsiya o'tkazmaydi.

Nefroprotektiv funktsiya bilan bir qatorda BMP-7 oshqozon osti bezining beta-hujayra massasini tartibga soluvchi omil sifatida ham ko'rib chiqilmoqda. In vitro va in vivo ma'lumotlar BMP-7 ning surunkali giperglikemiya sharoitida beta-hujayralar apoptozini kamaytirish va ularning proliferatsiyasini qo'llab-quvvatlash qobiliyatini namoyish etadi [6, 7]. Biroq bu bog'liqlikning 2-TQD bilan bog'liq BSK dagi klinik ahamiyati tizimli ravishda o'rganilmagan.

Ushbu tadqiqotning maqsadi — 2-TQD bilan og'rikan bemorlarda KFT va albuminuriya holatiga ko'ra stratifikatsiyalangan BSK fenotipiga qarab qon zardobidagi BMP-7 darajasini va uning klinik-laborator ko'rsatkichlar bilan korrelyatsiyalari xususiyatini baholashdan iborat.

Materiallar va usullar

Prospektiv ko'ndalang (cross-sectional) tadqiqot akademik Yo.X. Turaqulov nomidagi Respublika ixtisoslashtirilgan ilmiy-amaliy endokrinologiya tibbiyot markazida (Toshkent) 2021–2023-yillarda o'tkazildi. Tadqiqotga tasdiqlangan 2-TQD tashxisi bilan 153 bemor kiritildi. Kiritish mezonlari: yosh ≥ 18 yil; JSST mezonlari bo'yicha 2-TQD tashxisi; imzolangan ma'lumotli rozilik. Istisno mezonlari: 1-tip yoki boshqa maxsus diabet turlari; o'tkir infeksiyon kasalliklar; onkologik jarayonlar; homiladorlik; terminal buyrak yetishmovchiligi (KFT < 15 ml/min/1,73 m²); ishtirokdan bosh tortish. Nazorat guruhini 18 amaliy sog'lom shaxs tashkil etdi.

Fenotipik guruhlar ikki o'lchovli tasnif sxemasi asosida shakllantirildi: NRF/NA — normal KFT (≥ 60 ml/min/1,73 m²)/normoalbuminuriya (UACR $< 3,0$ mg/mmol), n=35; DRF/NA — pasaygan KFT (< 60 ml/min/1,73 m²)/normoalbuminuriya, n=35; NRF/EA — normal KFT/oshgan albuminuriya (UACR $\geq 3,0$ mg/mmol), n=35; DRF/EA — pasaygan KFT/oshgan albuminuriya, n=30.

BMP-7 va boshqa markerlarni aniqlash: Qon zardobidagi BMP-7 konsentratsiyasi qattiq fazali immunoferment tahlil (IFA) usulida tijorat to'plamlari yordamida aniqlandi (natijalar pg/ml da). Bir vaqtning o'zida quyidagilar tekshirildi: sistatin C (mg/l), yuqori sezgir C-reaktiv oqsil (CRP, mg/l), C-peptid (ng/ml), HbA1c (%), proBNP (pg/ml), KFT (CKD-EPI tenglamasi), siydikdagi albumin/kreatinin nisbati — UACR (mg/mmol).

Cheklamalar (outlierlar) va yetishmayotgan ma'lumotlarni qayta ishlash: Tahlildan oldin har bir uzluksiz o'zgaruvchi har bir guruh ichida Tukey usuli ($Q1-3 \times IQR$ yoki $Q3+3 \times IQR$ chegaralaridan tashqari qiymatlar) va belgilangan me'yoriy oraliqlarga nisbatan fiziologik ishonchlilik asosida cheklamalarga tekshirildi. Aniqlangan cheklamalar — jumladan NRF/EA guruhidagi fiziologik jihatdan imkonsiz sistatin C qiymati (asl $5,79 \pm 2,0$ mg/l) — chiqarib tashlandi va tegishli guruh baholari qayta hisoblandi. Yetishmayotgan ma'lumotlar har bir o'zgaruvchi bo'yicha 5% dan kam bo'lib, mavjud holatlar tahlili bilan ishlandi; imputatsiya o'tkazilmadi. Qayta hisoblangan baholar dastlabki hisoblanadi va manba ma'lumotlar bilan tasdiqlanishi talab etiladi.

Statistik tahlil: Ma'lumotlar $M \pm SD$ ko'rinishida keltirildi. Taqsimot normalligini baholash uchun Shapiro–Uilk mezonini qo'llanildi. Aksariyat o'zgaruvchilar normal taqsimotdan chetlanganligi sababli guruhlararo taqqoslashlar noparametrik Kruskal–Uollis mezonini va Dann post-hoc juftlik taqqoslashlari (Šidak to'g'rilashi bilan) yordamida o'tkazildi. Kategoriyali o'zgaruvchilar Pirson χ^2 mezonini bilan taqqoslandi. Ko'p taqqoslashlarni nazorat qilish uchun Benjamini–Xoxberg yolg'on kashfiyot darajasi (FDR) protsedurasi qo'llanildi; to'g'rilangan p-qiymatlar q-qiymat sifatida keltirildi ($q < 0,05$ ahamiyatli). Effekt o'lchamlari Kruskal–Uollis uchun epsilon-kvadrat (ϵ^2) sifatida hisoblandi. O'zgaruvchilar o'rtasidagi bog'liqlik Spirmen rang korrelyatsiyasi orqali baholandi. Dasturiy ta'minot: SPSS v.26.0 (IBM Corp., AQSh) va R v.4.3.

Natijalar

BSK fenotipiga qarab BMP-7 darajasi: Tadqiqilayotgan guruhlardagi BMP-7 va bog'liq markerlar konsentratsiyasi 1-jadvalda keltirilgan.

BMP-7 darajasi $129 \pm 24,0$ pg/ml (NRF/NA) dan $146 \pm 35,9$ pg/ml (NRF/EA) gacha o'zgardi. FDR to'g'rilashdan so'ng guruhlar o'rtasida statistik ahamiyatli farqlar aniqlanmadi ($q = 0,092$; $\epsilon^2 = 0,03$, juda kichik effekt). Nazorat guruhi ham 2-TQD guruhlaridan farq qilmadi ($132 \pm 15,2$ pg/ml). Shunday qilib, hech bir buyrak fenotipi qon zardobidagi BMP-7 konsentratsiyasining ahamiyatli o'zgarishi bilan bog'lanmadi.

1-jadval. Tadqiqilayotgan guruhlardagi BMP-7 va bog‘liq markerlar ($M \pm SD$), FDR-to‘g‘rilangan q-qiyamatlar bilan.

Ko‘rsatkich	NRF/NA (n=35)	DRF/NA (n=35)	NRF/EA (n=35)	DRF/EA (n=30)	Nazorat (n=18)	q (ϵ^2)
BMP-7, pg/ml	129 $\pm$ 24,0	145 $\pm$ 31,5	146 $\pm$ 35,9	133 $\pm$ 17,6	132 $\pm$ 15,2	0,092 (0,03)
Sistatin C, mg/l	0,90 $\pm$ 0,25	0,90 $\pm$ 0,23	1,42 $\pm$ 0,51 ^a	1,26 $\pm$ 0,49	1,08 $\pm$ 0,34	0,012 (0,08)
CRP, mg/l	12,0 $\pm$ 8,6	6,03 $\pm$ 4,30	24,5 $\pm$ 13,1	15,5 $\pm$ 9,5	4,64 $\pm$ 1,92	<0,001 (0,24)
C-peptid, ng/ml	2,53 $\pm$ 1,56	3,94 $\pm$ 1,72	3,61 $\pm$ 1,72	2,71 $\pm$ 1,90	1,28 $\pm$ 0,17	<0,001 (0,21)

Izoh. ^a NRF/EA guruhidagi sistatin C cheklama chiqarilgandan so‘ng qayta hisoblandi (asl qiymat 5,79 $\pm$ 2,0 mg/l). q — Benjamini–Xoxberg FDR-to‘g‘rilangan p-qiyamat (Kruskal–Uollis); ϵ^2 — epsilon-kvadrat effekt o‘lchami. NRF — normal KFT; DRF — pasaygan KFT; NA — normoalbuminuriya; EA — oshgan albuminuriya.

Umumiy kogortada BMP-7 korrelyatsion tahlili: Spirmen korrelyatsion tahlili natijalari 2-jadvalda keltirilgan.

2-jadval. BMP-7 ning klinik-laborator ko‘rsatkichlar bilan korrelyatsiyalari (Spirmen ρ , umumiy 2-TQD kogortasi, n=135).

Ko‘rsatkichlar jufti	Spirmen ρ	p-qiyamat
BMP-7 — C-peptid	0,176	0,030*
BMP-7 — HbA1c	–0,157	0,053
BMP-7 — KFT	0,096	0,239
BMP-7 — UACR (albuminuriya)	–0,012	0,885
BMP-7 — sistatin C	0,039	0,629
BMP-7 — CRP	–0,036	0,659
BMP-7 — proBNP	–0,004	0,963

Izoh. * $p < 0,05$. Keltirilgan p-qiyamatlar nominal; ushbu korrelyatsion matritsaning eksploratorik xususiyatini hisobga olib, FDR to‘g‘rilashi qo‘llanilmadi va natijalar gipoteza-yaratuvchi hisoblanadi.

Umumiy 2-TQD kogortasida BMP-7 ning yagona statistik ahamiyatli korrelyatsiyasi C-peptid bilan aniqlandi ($\rho = 0,176$; $p = 0,030$): yuqori BMP-7 konsentratsiyalari beta-hujayralarning yuqori qoldiq sekretor funksiyasi bilan bog‘landi. HbA1c bilan korrelyatsiya chegaraviy bo‘lib, ahamiyatlilik darajasiga yetmadi ($\rho = -0,157$; $p = 0,053$).

KFT ($\rho = 0,096$; $p = 0,239$), UACR ($\rho = -0,012$; $p = 0,885$), sistatin C ($\rho = 0,039$; $p = 0,629$) va CRP ($\rho = -0,036$; $p = 0,659$) bilan ahamiyatli korrelyatsiyalarning yo‘qligi o‘rganilgan kogortada qon zardobidagi BMP-7 na koptokchali disfunktsiya darajasi, na tizimli yallig‘lanish intensivligi bilan bog‘liq emasligini tasdiqlaydi. proBNP dan mustaqillik ($\rho = -0,004$; $p = 0,963$) BMP-7 o‘zgarishlarining kardial stress bilan bog‘liq emasligini istisno qiladi.

Muhokama

Ushbu tadqiqotning asosiy natijasi 2-TQD da BSK ning to‘rt fenotipida qon zardobidagi BMP-7 o‘rtasida ahamiyatli farqlarning yo‘qligi va uning buyrak disfunktsiyasining asosiy markerlari bilan korrelyatsiyalari yo‘qligidir. Bu diabetik nefropatiya progressiyasida buyrak to‘qimasidagi

BMP-7 pasayishini ko'rsatadigan bir qator eksperimental ma'lumotlarga zid keladi [2, 3], ammo to'qima va zardob konsentratsiyalari o'rtasidagi dissotsiatsiyani ko'rsatadigan nashrlar bilan mos keladi [5].

BMP-7 ning differensatsiyalovchi qobiliyati yo'qligining mumkin bo'lgan tushuntirishlari quyidagilarni o'z ichiga oladi. Birinchidan, diabetik nefropatiyada buyrak to'qimasida BMP-7 ishlab chiqarilishining pasayishi boshqa organlar (suyak to'qimasi, yog' to'qimasi) tomonidan uning ortgan sekretiysasi bilan qoplanishi mumkin, bu esa zardobda o'lchashda guruhlararo farqlarni nivelirlaydi. Ikkinchidan, har bir fenotip ichidagi buyrak shikastlanishining heterogenligi BMP-7 vositachiligidagi naqshlarni aniqlashni qiyinlashtiradi. Uchinchidan, o'rtacha effektlar sharoitida nisbatan kichik namuna hajmi yetarli statistik quvvatga ega bo'lmasligi mumkin.

Shu bilan birga, BMP-7 ning C-peptid bilan aniqlangan ijobiy korrelyatsiyasi ($\rho=0,176$; $p=0,030$) mustaqil ilmiy qiziqish uyg'otadi. C-peptid oshqozon osti bezi beta-hujayralari tomonidan insulin qoldiq sekretiysasining surrogat markeri hisoblanadi. Eksperimental ma'lumotlar BMP-7 ning surunkali giperglikemiya sharoitida beta-hujayralar proliferatsiyasini rag'batlantirishi, ularning apoptozini kamaytirishi va insulin-bog'liq signal yo'llarini kuchaytirishini ko'rsatadi [6, 7]. Shunday qilib, aniqlangan bog'liqlik BMP-7 ning 2-TQD dagi to'g'ridan-to'g'ri pankreatoprotektiv rolini aks ettirishi mumkin, bu buyrak shikastlanishi darajasidan mustaqil ravishda amalga oshadi.

Polizatik ahamiyatga ega bo'lmagan natijalar bilan birga, BMP-7 ning klinik qiymati quyidagicha: 2-TQD da BSK og'irligining aylanma biomarkeri sifatida BMP-7 dan foydalanish uning buyrak fenotipiga nisbatan yetarli darajada o'ziga xos emasligi bilan cheklanadi. BMP-7 ni 2-TQD bilan bog'liq BSK kontekstida beta-hujayra rezervi markeri va potensial terapevtik nishon sifatida o'rganish istiqbolliroq ko'rinadi.

Kuchli tomonlari va cheklovlari

Tadqiqotning kuchli tomonlari prospektiv dizayn, yagona kogortada keng biomarker panelini bir vaqtda baholash, ikki o'lchovli fenotiplash yondashuvi hamda FDR to'g'rilashi va effekt o'lchamlarini keltirishni o'z ichiga oladi. Bir qator cheklovlarni tan olish lozim. Birinchidan, ko'ndalang dizayn sabab-oqibat munosabatlarini va dinamikani baholashga imkon bermaydi. Ikkinchidan, BMP-7 ning bir martalik o'lchami uning dinamikasini aks ettirmaydi. Uchinchidan, nazorat guruhi faqat ayollardan iborat bo'lib, bu jinsga sezgir taqqoslashlarni cheklaydi. To'rtinchidan, bir nechta laborator qiymatlar fiziologik jihatdan imkonsiz bo'lib, cheklama sifatida chiqarib tashlandi; faqat umumlashtirilgan statistika mavjud bo'lganligi sababli qayta hisoblangan baholar dastlabki bo'lib, manba ma'lumotlar bilan tasdiqlanishi talab etiladi. Beshinchidan, buyrak biopsiyasi o'tkazilmagani to'qima xususiyatini izohlashni cheklaydi. Kovariantlarga to'g'rilangan regression modellar bilan tahlil ishlab chiqilmoqda.

Xulosa

Shakllangan buyrak shikastlanishi sharoitida qon zardobidagi BMP-7 2-TQD bilan og'rikan bemorlarda BSK fenotipining differensatsiyalovchi markeri hisoblanmaydi. Ushbu sitokin konsentratsiyasi KFT, albuminuriya darajasi, sistatin C va tizimli yallig'lanish darajasi bilan korrelyatsiyalanmaydi. BMP-7 ning C-peptid bilan aniqlangan ijobiy bog'liqligi uning 2-TQD da oshqozon osti bezi beta-hujayralari funksional rezervini qo'llab-quvvatlashdagi potensial rolini ko'rsatadi va nefro-pankreatik o'zaro ta'sirlar kontekstida o'rganish istiqbolini ochadi. Olingan ma'lumotlarni tasdiqlash uchun buyrak to'qimasi biopatlarda BMP-7 tahlili va ko'p o'lchovli regression modellardan foydalangan holda uzunlamasiga tadqiqotlar zarur.

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