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Article/Review

ASSOCIATION OF THE Gln27Glu POLYMORPHISM OF THE β2-ADRENOCEPTOR GENE WITH LIPID METABOLISM FEATURES IN PATIENTS WITH BRONCHIAL ASTHMA

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Abstract.

Relevance. Considering the key role of β_2-adrenoceptors in bronchodilation mechanisms, as well as their involvement in the regulation of metabolic processes, the analysis of genetic variants of the β_2-adrenoceptor gene is of particular importance for understanding the pathogenesis of bronchial asthma, especially in the presence of concomitant metabolic disorders, including dyslipidemia and obesity. **Objective.** To determine the association between the Gln27Glu polymorphism of the β_2-adrenoceptor gene and lipid metabolism parameters in patients with bronchial asthma, taking obesity phenotype into account. **Materials and Methods.** The study included 81 patients with bronchial asthma. The diagnosis was established according to GINA criteria. The mean age of the patients was 42.5 ± 1.41 years, with a mean disease duration of 10.1 ± 0.73 years. Total cholesterol, triglycerides, low-density and high-density lipoproteins, and atherogenic index were analyzed. Genotyping of the Gln27Glu polymorphism of the β_2-adrenoceptor gene was performed using PCR. **Results.** The highest total cholesterol level was observed in obese patients with the Gln27Gln genotype (6.44 ± 0.17 mmol/L), whereas in obese patients with the Gln27Glu genotype it was significantly lower (5.69 ± 0.16 mmol/L; $p < 0.01$). Similarly, LDL levels were highest in obese patients with the Gln27Gln genotype (3.91 ± 0.13 mmol/L), compared to those with the Gln27Glu genotype ($p < 0.01$). HDL levels were similar across all groups (1.19–1.51 mmol/L) without statistically significant differences ($p > 0.05$). The atherogenic index was highest in the obese Gln27Gln group (4.45 ± 0.18), while in the Gln27Glu group it was significantly lower (3.29 ± 0.16; $p < 0.001$). **Conclusion.** The Gln27Gln genotype in the presence of obesity is associated with adverse lipid profile changes, including elevated total cholesterol, triglycerides, LDL, and atherogenic index, indicating an increased atherosclerotic risk in this patient group. Final Remark. The Gln27Gln genotype combined with obesity may serve as a potential marker of unfavorable prognosis characterized by lipid metabolism disturbances and an increased risk of cardiovascular complications.

Key words: bronchial asthma, Gln27Glu polymorphism, β_2-adrenoceptor, lipid metabolism, obesity.

Bronxial astma (BA) — bu nafas yo‘llarining surunkali yallig‘lanish kasalligi bo‘lib, uning rivojlanishi va klinik kechishida tashqi hamda ichki (shu jumladan, genetik) omillar muhim rol o‘ynaydi [1,2,4,6]. BAning patogenezida ishtirok etuvchi nomzod genlardan biri bu β2-adrenoretseptor (ADRB2) genidir. U bronxlar silliq mushaklarining bo‘shashuvini ta’minlaydigan retseptorni kodlaydi. ADRB2 genining Gln27Glu (rs1042714) polimorfizmi nafaqat β2-agonistlarga retseptor sezuvchanligiga [3], balki moddalar almashinuviga, jumladan, lipid almashinuviga ham ta’sir ko‘rsatishi mumkin [7,9]. Lipid almashinuvi buzilishlari — giperxolesterinemiya, triglitseridlar darajasining oshishi, aterogen dislipidemiya shakllari — ko‘pincha BA bilan birga kechadi [5,8], ayniqsa ortiqcha vazn va semizlik bilan og‘rigan bemorlarda.

Gln27Glu polimorfizmi kabi genetik belgilarni va ularning lipid profili bilan bog‘liqligini o‘rganish metabolik asoratlar xavfi yuqori bo‘lgan bemorlar guruhini aniqlash imkonini beradi. Bu esa davolash va profilaktikaga individual yondashuvni ishlab chiqishga yordam beradi.

Tadqiqot maqsadi. ADRB2 genining Gln27Glu polimorfizmi va BA bilan og‘rigan bemorlarda, semizlik fenotipini hisobga olgan holda, lipid almashinuvi xususiyatlari o‘rtasidagi o‘zaro bog‘liqlikni aniqlash.

Materiallar va usullar. Tadqiqotga o‘zbek millatiga mansub 128 nafar shaxs jalb etildi, ulardan 81 nafari BA bilan og‘rigan bemorlar edi. BA tashxisi JSSTning xalqaro tasnifi va GINA mezonlariga muvofiq qo‘yildi. BA bilan og‘rigan bemorlarning o‘rtacha yoshi 42,5±1,41 yoshni, kasallik davomiyligi esa o‘rtacha 10,1±0,73 yilni tashkil etdi. Ular orasida 36 nafar erkak (44%) va 45 nafar ayol (56%) bor edi. Taqqoslash uchun nazorat guruhini yosh va jins jihatdan mos keluvchi 47 nafar sog‘lom shaxs tashkil etdi.

BA bilan og‘rigan bemorlar tana vazni indeksiga (TVI) qarab ikki guruhga bo‘lindi: asosiy guruh — TVI > 30 kg/m² bo‘lgan 37 nafar bemor; ichki nazorat guruhi — TVI < 30 kg/m² bo‘lgan 44 nafar bemor. Ushbu guruhda o‘rtacha TVI 32,50 ± 0,19 kg/m² ni tashkil etdi.

Barcha ishtirokchilar quyidagi klinik-instrumental tekshiruvlardan o‘tkazildi: spiroometriya (standart metodika bo‘yicha), quyidagi ko‘rsatkichlar baholandi: o’pka jadal hayotiy sig‘im, hayotiy sig‘im, 1 soniyada jadal chiqarilgan havo hajmi, Tiffno indeksi, maksimal ekspirator tezliklar (MOS75, MOS50, MOS25), shuningdek, bronxolitik testdan keyingi bronxial obstruktsiyaning qaytarligi. Antropometrik o‘lchovlar: bo‘y, tana vazni, bel aylanasining uzunligi, TVI (kg/m²) hisoblash. Biokimyoviy venoz qon tahlillari: triglitseridlar (TG), umumiy xolesterin, yuqori zichlikdagi lipoproteidlar xolesterini (XS-YuZLP) va past zichlikdagi lipoproteidlar xolesterini (XS-PZLP) darajasi aniqlandi.

ADRB2 genining Gln27Glu polimorfizmi quyidagicha genotiplashtirildi:

DNK butun qon namunalaridan Diatom™ DNA Prep 200 (MChJ «Izogen Laboratoriyasi») to‘plami yordamida standart protokol asosida ajratib olindi. ADRB2 geni fragmenti polimeraza zanjiri reaksiyasi (PZR) yordamida quyidagi maxsus praymerlar bilan ko‘paytirildi: Forward: 5’-CCGGACCACGACGTCACCCAG-3’. Reverse: 5’-CCAGTGAAGTGATGAAGTAGTT-3’. PZR tahlillari GenePak™ PCR Core (MChJ «Izogen Laboratoriyasi») to‘plami yordamida amalga oshirildi.

Statistik tahlil Microsoft Excel-2010 dasturining statistik funksiyalari yordamida bajarildi. Ma’lumotlar o‘rtacha arifmetik qiymat (M) va o‘rtacha xatolik (m) ko‘rinishida keltirildi. Guruhlar orasidagi farqlarning ishonchliligi tegishli statistik mezonlar yordamida baholandi.

Natijalar va muhokamasi. Quyidagi lipid almashinuv ko‘rsatkichlari o‘rganildi: umumiy xolesterin, triglitseridlar, XS-YZLP va XS-PZLP, shuningdek, aterogenlik koeffitsienti — bu ko‘rsatkichlar semirish mavjudligi yoki yo‘qligiga, shuningdek, Gln27Gln va Gln27Glu genotiplariga ega BA bemorlarida, shuningdek nazorat guruhida tahlil qilindi (jadval).

Jadval-1

ADRB2 geni turli genotiplari va semizlik holatiga ega bo‘lgan bemorlarda lipid profili

Ko‘rsatkich	Tadqiqot guruhlari				
	Semizlik Gln27Gln (n=19)	Semizlik Gln27Glu (n=17)	Semizliksiz Gln27Gln (n=23)	Semizliksiz Gln27Glu (n=19)	Nazorat (n=47)
Umumiy xolesterin (mmol/l)	6,44 ± 0,17 o***	5,69 ± 0,16	5,21 ± 0,14 ***	5,05 ± 0,15 **	4,41 ± 0,41
Triglitseridlar (mmol/l)	2,28 ± 0,12 o**	1,73 ± 0,09	1,55 ± 0,11 ***	1,42 ± 0,10 *	1,32 ± 0,21
PZLP (mmol/l)	3,91 ± 0,13 o**	3,22 ± 0,11	3,02 ± 0,09 ***	2,87 ± 0,08 *	2,53 ± 0,33
YuZLP (mmol/l)	1,19 ± 0,06	1,33 ± 0,05	1,44 ± 0,05	1,52 ± 0,06	1,32 ± 0,12
Aterogenlik koeff.	4,45 ± 0,18 o***	3,29 ± 0,16	2,64 ± 0,12 ***	2,43 ± 0,10	2,81 ± 0,32

Izoh: o — semizlik bilan guruhda Gln27Glu genotipi bilan solishtirganda ishonchli farq; *— p < 0,05, ** — p < 0,01, *** — p < 0,001 nazorat guruhi bilan solishtirganda ishonchli farq.

Umumiy xolesterin darajasining eng yuqori ko‘rsatkichi semizlikka va Gln27Gln genotipiga ega bemorlarda kuzatildi (6,44±0,17 mmol/l). Semirishga ega Gln27Glu genotipiga ega bemorlarda esa bu ko‘rsatkich pastroq (5,69±0,16 mmol/l; p<0,01). Semirishsiz bemorlar guruhida umumiy

xolesterin darajalari yanada past bo‘lib, Gln27Gln uchun 5,21±0,14 mmol/l, Gln27Glu uchun esa 5,05±0,15 mmol/l ni tashkil etdi — bu farq genotiplar o‘rtasida statistik jihatdan ahamiyatli emas (p>0,05). Nazorat guruhi eng past xolesterin darajasiga ega bo’ldi (4,41±0,41 mmol/l), bu semirishga ega (p<0,001) va semirishsiz (p<0,01) bemorlar guruhlariga qaraganda statistik jihatdan sezilarli darajada past. Shunday qilib, semirish umumiy xolesterin darajasining oshishiga olib keladi, ayniqsa Gln27Gln genotipiga ega bo‘lgan bemorlarda.

Triglitseridlar darajasi ham semirishga ega Gln27Gln genotipiga ega bemorlarda yuqori bo‘lib (2,28±0,12 mmol/l), Gln27Glu genotipiga ega bemorlarda esa bu daraja pastroq (1,73±0,09 mmol/l), lekin genotiplar o‘rtasidagi farq statistik jihatdan ahamiyatli emas (p>0,05). Semirishsiz BA bemorlarida triglitseridlar darajasi yanada past bo‘lib, Gln27Gln uchun 1,55±0,11 mmol/l, Gln27Glu uchun esa 1,42±0,10 mmol/l ni tashkil etdi; bu farq ham ahamiyatli emas (p>0,05). Nazorat guruhi eng past triglitseridlar darajasiga ega bo’ldi (1,32±0,21 mmol/l), bu semirishga ega guruh ko’rsatkichlariga nisbatan sezilarli darajada past (p<0,001), semirishsiz guruhga nisbatan esa sezilarli farq bor (p<0,05). Demak, triglitseridlar darajasining oshishi asosan semirish bilan bog‘liq, genotip esa bunga sezilarli ta’sir ko‘rsatmaydi.

PZLP darajasi BA va semizlikka ega bo‘lgan Gln27Gln genotipli bemorlarda eng yuqori (3,91±0,13 mmol/l) bo’ldi. Shu guruhdagi Gln27Glu genotipiga ega bemorlarda PZLP darajasi ancha past (3,22±0,11 mmol/l), va bu farq statistik jihatdan ahamiyatli (p<0,01). Semizliksiz bemorlar guruhida PZLP darajasi pastroq (mos ravishda 3,02±0,09 va 2,87±0,08 mmol/l), ammo bu yerda genotiplar o‘rtasidagi farq ahamiyatli emas (p>0,05). Nazorat guruhi eng past PZLP darajasiga ega bo’ldi (2,53±0,33 mmol/l), bu semirishga ega guruhga nisbatan sezilarli darajada past (p<0,001), semizliksiz guruhga nisbatan esa sezilarli past (p<0,05). Demak, PZLP darajasining oshishi semirish bilan bog‘liq bo‘lib, ayniqsa Gln27Gln genotipi bilan yanada kuchayadi, bu esa ateroskleroz xavfini oshiradi.

YuZLP miqdori barcha guruhlarda deyarli bir xil (1,19–1,51 mmol/l) bo‘lib, bunda statistik jihatdan ahamiyatli farqlar kuzatilmadi (p>0,05). Nazorat guruhi BA bemorlariga nisbatan YuZLP darajasida farq ko‘rsatmadi. Demak, YuZLP darajasi ushbu tanlovda genotip hamda semizlik bilan bog‘liq emas.

Aterogenlik koeffitsienti eng yuqori darajaga ega bo‘lgan guruh — bu semirishga ega Gln27Gln genotipli BA bemorlaridir (4,45±0,18). Shu guruhdagi Gln27Glu genotipiga ega bemorlarda aterogenlik koeffitsienti 3,29±0,16 bo‘lib, bu Gln27Gln genotipiga ega bemorlari ko’rsatkichlariga nisbatan sezilarli darajada past (p<0,001). Semirishsiz guruhda bu ko‘rsatkichlar pastroq (mos ravishda 2,64±0,12 va 2,43±0,10), va genotiplar o‘rtasidagi farq ahamiyatli emas (p>0,05). Nazorat guruhida aterogenlik koeffitsienti 2,81±0,32 ni tashkil etdi, bu semirishga ega Gln27Gln bemorlariga nisbatan sezilarli darajada past (p<0,001), semirishsiz guruhlarga nisbatan esa farq sezilmaydi (p>0,05). Demak, aterogenlik koeffitsientining oshishi semirish va Gln27Gln genotipi bilan bog‘liq bo‘lib, bu yurak-qon tomir kasalliklari xavfining oshishini ko‘rsatadi.

Xulosa:

1. ADRB2 genining Gln27Gln genotipi semizlik mavjud bo‘lgan holatlarda lipid almashinuvi ko‘rsatkichlari bilan bog‘liq: bunda umumiy xolesterin, triglitseridlar, past zichlikdagi lipoproteidlar va aterogenlik koeffitsientining oshishi kuzatiladi. Bu o‘zgarishlar ushbu bemorlar guruhida yuqori aterosklerotik xavf mavjudligini ko‘rsatadi.

2. ADRB2 genining Gln27Glu genotipi qisman protektor ta’sirga ega bo‘lib, semirishning lipid profiliga salbiy ta’sirini kamaytiradi, ammo metabolik xavflarni to‘liq bartaraf eta olmaydi.

3. YuZLP darajasi boshqa lipid fraksiyalaridan farqli o‘laroq, genotiplar va kichik guruhlar o‘rtasida ishonchli farq ko‘rsatmadi, bu esa ushbu ko‘rsatkichning genetik va fenotipik ta’sirlarga nisbatan sezuvchanligi pastligini bildiradi.

Shunday qilib, tadqiqotimiz natijalari ADRB2 genining Gln27Glu polimorfizmini BA bilan kasallangan bemorlarda metabolik ko‘rsatkichlarni baholashda genetik omillarni hisobga olish muhimligini ta’kidlaydi. Gln27Gln genotipi va semizlik kombinatsiyasi lipid almashinuvi buzilishi bilan kechuvchi va yurak-qon tomir asoratlari xavfini oshiruvchi salbiy prognoz belgisi bo‘lib xizmat qilishi mumkin. Shu sababli, BA bilan kasallangan bemorlarni davolashda individual yondashuv nafaqat fenotipik xususiyatlarni, balki genetik moyillikni baholashni ham o‘z ichiga olishi zarur. Bu esa

profilaktik choralarni va metabolik yo‘naltirilgan terapiya strategiyalarini optimallashtirish imkonini beradi.

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