

POTENTIAL SIGNIFICANCE OF BRADYKININ 2 RECEPTOR AND/OR ANGIOTENSIN-CONVERTING ENZYME GENOTYPING IN KIDNEY TRANSPLANT RECIPIENTS

**Katarina Danković¹, Nikola Stefanović², Ivana Damnjanović²,
Aleksandra Catić-Đorđević², Radmila Veličković-Radovanović^{3,4},
Tatjana Cvetković⁵**

¹ University of Niš - Faculty of Medicine, Niš, Serbia

² University of Niš - Faculty of Medicine, Department of Pharmacy, Niš, Serbia

³ Clinic of Nephrology, Clinical Center Nis, Nis, Serbia

⁴ University of Niš - Faculty of Medicine, Department of Pharmacology with toxicology, Niš, Serbia

⁵ University of Niš - Faculty of Medicine, Department of Biochemistry, Niš, Serbia

Kidney transplantation (Tx) remarkably improved short-term outcomes in patients with end-stage kidney disease, but growing evidence indicates that identifying the biomarkers associated with long-term outcomes is of utmost importance. Bradykinin (BK) is considered to exert renoprotective and cardioprotective effects, which are mainly mediated by the activation of BK type 2 receptor (B2R). It is commonly believed that the therapeutic benefits of angiotensin-converting enzyme (ACE) inhibitors derive more from inhibiting the inactivation of the kinins than by suppressing angiotensin II formation (1). The level of B2R expression is influenced by insertion/deletion (+9/-9) gene polymorphism in exon 1 of the B2R gene, while the plasma and tissue messenger RNA (mRNA) levels of the ACE are associated with a 287 base pairs insertion/deletion polymorphism in intron 16 (I/D) of the ACE gene. It has been assumed that the carriers of B2R +9 allele and ACE D allele have an increased risk for developing diabetes mellitus and chronic kidney disease respectively (2,3). The main goal of this study was to evaluate the potential association of B2R +9/-9 and ACE I/D gene polymorphisms with graft function [defined as estimated glomerular filtration rate, eGFR] in the period from 6 up to 36 months after Tx. The pharmacogenetic study enrolled 96 patients genotyped for B2R and ACE polymorphism. Linear regression analysis was performed to evaluate the potential influence of genetic factors along with demographic characteristics on eGFR values from 13 and up to 36 months. The obtained results reported that the B2R heterozygotes and +9/+9 genotype carriers had eGFR values that were less by 13.073 ($p < 0.001$) and 9.193 ($p < 0.001$) than those in -9/-9 genotype carriers. Besides B2R polymorphism, lower eGFR at 6 months, acute rejection, female gender, and advanced age were significant predictors of worse eGFR between 13 and 36 months. On contrary, ACE polymorphism did not express the significant influence on long-term eGFR values. The corresponding multivariate analysis confirmed that the +9 allele was associated with lower eGFR values compared to the carriers of both -9 alleles (-9/+9: $p < 0.001$; +9/+9: $p < 0.001$) even after adjusting for other significant covariates. Therefore, kidney transplant patients may potentially benefit from the introduction of ACE inhibitors into the therapy, especially +9 allele carriers, due to they are the most effective drugs nowadays in enhancing the kallikrein-kinin system through reducing the degradation of endogenous BK and enhancing the sensitivity of the B2R.

References

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POTENCIJALNI ZNAČAJ GENOTIPIZACIJE POLIMORFIZMA BRADIKININ TIP 2 RECEPTORA I/ILI POLIMORFIZMA ANGIOTENZIN KONVERTUJUĆEG ENZIMA KOD PACIJENATA SA TRANSPLANTIRANIM BUBREGOM

**Katarina Danković¹, Nikola Stefanović², Ivana Damnjanović²,
Aleksandra Catić-Đorđević², Radmila Veličković-Radovanović^{3,4},
Tatjana Cvetković⁵**

¹ Univerzitet u Nišu - Medicinski fakultet, Niš, Srbija

² Univerzitet u Nišu - Medicinski fakultet, Katedra za farmaciju, Niš, Srbija

³ Klinika za nefrologiju, Klinički centar Niš, Niš, Srbija

⁴ Univerzitet u Nišu - Medicinski fakultet, Katedra farmakologija sa toksikologijom,
Niš, Srbija

⁵ Univerzitet u Nišu - Medicinski fakultet, Katedra Biohemija, Niš, Srbija

Transplantacija bubrega (Tx) značajno je poboljšala kratkoročne ishode kod pacijenata sa krajnjim stadijumom bubrežne bolesti, međutim, rastući je broj dokaza koji ukazuju da je identifikacija biomarkera povezanih sa dugoročnim ishodima od velike važnosti. Bradikinin (BK) ispoljava renoprotektivne i kardioprotektivne efekte, koji su uglavnom posredovani aktivacijom BK receptora tipa 2 (B2R). Generalno se smatra da terapijski benefit inhibitora angiotenzin-konvertujućeg enzima (ACE) u većoj meri zavisi od inhibicije inaktivacije kinina nego od inhibicije formiranja angiotenzina II (1). Na nivo ekspresije B2R utiče polimorfizam insercije/delecije 9 baznih parova (+9/-9) u eksonu 1 B2R gena, dok su nivoi ACE informacione RNK (iRNK) u plazmi i tkivu povezani sa polimorfizmom insercije/delecije 287 baznih parova u intronu 16 (I/D) ACE gena. Pretpostavlja se da nosioci B2R +9 alela i ACE D alela imaju povećan rizik za razvoj dijabetes melitusa i hronične bolesti bubrega, respektivno (2,3). Glavni cilj ovog istraživanja bila je procena potencijalne povezanosti B2R +9/-9 i ACE I/D genskih polimorfizama sa funkcijom grafta [definisanom kao procenjena brzina glomerularne filtracije, eGFR] u periodu od 6 do 36 meseci nakon Tx. Farmakogenetska studija obuhvatila je 96 pacijenata genotipiziranih na B2R i ACE polimorfizam. Izvršena je linearna regresiona analiza da bi se procenio potencijalni uticaj genetskih faktora zajedno sa demografskim karakteristikama na eGFR vrednosti između 13 i 36 meseci. Dobijeni rezultati su pokazali da su B2R heterozigoti i nosioci +9/+9 genotipa imali eGFR vrednosti koje su bile manje za 13,073 ($p < 0,001$) i 9,193 ($p < 0,001$) u poređenju sa nosiocima -9/-9 genotipa. Osim B2R genskog polimorfizma, niže eGFR vrednosti u šestom mesecu nakon Tx, akutno odbacivanje, ženski pol i starost pacijenata su bili značajni prediktori nižih eGFR vrednosti između 13 i 36 meseci. Sa druge strane, ACE genski polimorfizam nije pokazao značajan uticaj na dugoročne eGFR vrednosti. Odgovarajuća multivarijantna analiza potvrdila je da je +9 alel povezan sa nižim eGFR vrednostima u poređenju sa nosiocima -9/-9 genotipa (-9/+9: $p < 0,001$; +9/+9: $p < 0,001$) čak i nakon prilagođavanja za druge značajne kovarijate. Stoga uvođenje ACE inhibitora u terapiju može biti od koristi kod pacijenata sa transplantiranim bubregom, posebno kod nosioca +9 alela, jer se u današnje vreme smatraju najefikasnijim lekovima u potencijaciji kalikrein-kinin sistema smanjenjem razgradnje endogenog BK i povećanjem osetljivosti B2R.

Literatura

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