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EFFECT OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS ON ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH MEMBRANOUS NEPHROPATHY

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The purpose of the study was to evaluate whether adding sodium-glucose cotransporter 2 inhibitors to standard therapy improves endothelial dysfunction in adults with idiopathic membranous nephropathy. In this prospective observational study, 42 phospholipase A2 receptor–positive patients were followed for 6 months and compared by treatment status (sodium-glucose cotransporter 2 inhibitor + standard therapy vs standard therapy alone); endothelial function (endothelium-dependent vasodilation and endothelium-independent vasodilation) and biomarkers (endothelin-1, and intercellular adhesion molecule-1, high-sensitivity C-reactive protein) were assessed together with urinary albumin-to-creatinine ratio. Add-on sodium-glucose cotransporter 2 inhibitor therapy was associated with a greater improvement in endothelium-dependent vasodilation ($p=0.032$), a larger reduction in albuminuria ($p<0.001$), and more pronounced decreases in endothelin-1 ($p<0.001$), intercellular adhesion molecule-1 ($p=0.002$), and high-sensitivity C-reactive protein ($p=0.036$), while endothelium-independent vasodilation and intima–media thickness did not differ significantly between groups. These findings suggest potential endothelial and antiproteinuric benefits of sodium-glucose cotransporter 2 inhibition in membranous nephropathy.

Key words: membranous nephropathy; sodium-glucose cotransporter 2 inhibitors, endothelial dysfunction, endothelium-dependent vasodilation, endothelin-1, intercellular adhesion molecule-1, albuminuria.

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ВПЛИВ ІНГІБІТОРІВ НАТРІЙ-ГЛЮКОЗНОГО КО-ТРАНСПОРТЕРА 2 ТИПУ НА ЕНДОТЕЛІАЛЬНУ ДИСФУНКЦІЮ У ПАЦІЄНТІВ З МЕМБРАНОЗНОЮ НЕФРОПАТІЄЮ

Метою дослідження було оцінити, чи покращує додавання інгібіторів натрій-глюкозного котранспортера 2-го типу до стандартної терапії ендотеліальну дисфункцію у дорослих з ідіопатичною мембранозною нефропатією. У цьому проспективному обсерваційному дослідженні 42 пацієнти з позитивним результатом на антитіла до рецептора фосфоліпази А2 спостерігалися протягом 6 місяців і порівнювалися за статусом лікування (інгібітор натрій-глюкозного котранспортера 2-го типу + стандартна терапія проти стандартної терапії окремо). Функція ендотелію (ендотелій-залежна та ендотелій-незалежна вазодилатація) та біомаркери (ендотелін-1, міжклітинна молекула адгезії-1, високочутливий С-реактивний білок) оцінювалися разом із співвідношенням альбуміну до креатиніну в сечі. Додаткова терапія інгібіторами натрій-глюкозного котранспортера 2-го типу супроводжувалася значним поліпшенням ендотелій-залежної вазодилатації ($p=0,032$), значним зниженням альбумінурії ($p<0,001$) та більш вираженим зниженням ендотеліну-1 ($p<0,001$), міжклітинної молекули адгезії-1 ($p=0,002$) та високочутливого С-реактивного білка ($p=0,036$), тоді як ендотелій-незалежна вазодилатація та товщина інтима-медіа істотно не відрізнялися між групами. Ці результати вказують на потенційні ендотеліальні та антипротеїнуричні переваги інгібування натрій-глюкозного котранспортера 2-го типу при мембранозній нефропатії.

Ключові слова: мембранна нефропатія, інгібітори натрій-глюкозного котранспортера 2-го типу, ендотеліальна дисфункція, ендотелій-залежна вазодилатація, ендотеліну-1, міжклітинна молекула адгезії-1, альбумінурія.

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Despite the introduction of multiple novel therapeutic strategies, glomerulonephritis remains a major contributor to end-stage renal disease (ESRD) worldwide [6, 7]. Current management is largely focused on controlling immune-mediated mechanisms of glomerular injury and providing optimized supportive care. One of the principal goals in nephrology is to slow the progression of chronic kidney disease (CKD) and delay or prevent the need for renal replacement therapy; however, this objective has not yet been fully achieved, as glomerulonephritis continues to be a leading cause of ESRD.

Within this spectrum of diseases, primary membranous nephropathy (PMN) is the most common cause of idiopathic nephrotic syndrome in nondiabetic adults, accounting for approximately 20–37 % of cases worldwide [2]. Importantly, even in patients with PMN who achieve both proteinuric and serological remission, residual endothelial dysfunction may persist. This observation highlights an unmet need for adjunctive therapeutic strategies that target vascular and endothelial pathways beyond traditional immunosuppressive approaches [9].

Given that albuminuria is a hallmark of glomerulonephritis, sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as a promising option for supportive therapy in this patient population [3]. Although SGLT2 inhibitors were initially developed for the treatment of type 2 diabetes mellitus [1], subsequent studies have demonstrated significant cardiovascular and renal protective effects that are independent of glycemic control [5, 10].

SGLT2 inhibitors contribute to improvements in systemic endothelial function. This effect has been demonstrated in patients with type 2 diabetes mellitus receiving dapagliflozin in combination with metformin, as well as in experimental models of diabetic rats treated with empagliflozin. It is suggested that these effects are mediated predominantly not by increased expression of endothelial nitric oxide synthase (eNOS), but rather by improved endothelial cell viability, attenuation of cellular senescence and inflammatory activity, and reduction of oxidative damage within the NO/cGMP signaling cascade [4, 8].

Similar mechanisms are also relevant at the renal level, since endothelial dysfunction of the renal vasculature plays a pivotal role in the pathogenesis of diabetic kidney disease. In this context, the beneficial effects of SGLT2 inhibitors on the endothelium may help slow the progression of declining renal function. Chronic kidney disease is characterized by profound systemic endothelial dysfunction, manifested, in particular, by impaired flow-mediated vasodilation. Studies evaluating the impact of SGLT2 inhibitors on endothelial dysfunction in primary membranous nephropathy are limited.

The purpose of the study was to investigate the effects of SGLT2 inhibitors on endothelial dysfunction at baseline and after therapy, with a particular focus on functional parameters of endothelium-dependent vasodilation.

Materials and methods. This prospective observational study was conducted at the Educational Therapy Clinic of Azerbaijan Medical University from February 2023 to May 2025. A total of 42 adult patients with idiopathic membranous nephropathy (IMN) were enrolled. Diagnosis was confirmed in all participants by renal biopsy and positivity for anti-phospholipase A2 receptor (PLA2R) antibodies. Participants completed structured questionnaires approved by the Ministry of Health of the Republic of Azerbaijan to collect standardized demographic and lifestyle data (including age, sex, smoking status, dietary habits, and physical activity).

Treatment was initiated according to the standard clinical protocol for primary membranous nephropathy, in accordance with KDIGO recommendations and national clinical guidelines. Standard therapy included supportive nephroprotective treatment consisting of renin–angiotensin–aldosterone system (RAAS) blockade (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), blood pressure control, statin therapy when indicated, anticoagulation in patients with high thrombotic risk, and dietary sodium/protein restriction. In selected patients with nephrotic syndrome and high risk of disease progression, immunosuppressive therapy (e.g., corticosteroids and/or cyclophosphamide or calcineurin inhibitors) was prescribed according to clinical indications.

Participants were allocated into two groups depending on whether a sodium–glucose cotransporter-2 inhibitor was added to the standard therapy. Group allocation was performed non-randomly based on clinical decision-making and physician discretion, taking into account patient eligibility, contraindications, and informed consent.

Group 1 (n=27) received an SGLT-2 inhibitor in addition to standard therapy: 13 patients were treated with dapagliflozin (Forxiga, AstraZeneca, United Kingdom), film-coated tablets, 10 mg once daily, administered orally for a duration of 6 months; 14 patients received empagliflozin (Jardiance, Boehringer Ingelheim, Germany), film-coated tablets, 10 mg once daily, administered orally for a duration of 6 months. Group 2 (n=15) received standard therapy alone without SGLT-2 inhibitors.

Exclusion criteria included severe treatment-related complications, secondary (type II) membranous nephropathy, phospholipase A2 receptor (PLA2R) negativity, significant comorbidities, a history of hypersensitivity or contraindications to SGLT-2 inhibitors, and age under 18 years.

Clinical and laboratory assessments were conducted at baseline and repeated after six months of follow-up. Renal function was evaluated using estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Serum creatinine levels were measured using an enzymatic colorimetric method on an automated biochemical analyzer (Hospitex Diagnostics (Switzerland) with microplate incubator Stat Fax 2200 (Awareness Technology, USA)), in accordance with the manufacturer's instructions and internal laboratory quality control standards. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.

Urinary albumin and creatinine concentrations were determined in spot urine samples collected in the morning. Urinary albumin was measured using an immunoturbidimetric assay, while urinary creatinine was assessed using a kinetic Jaffe or enzymatic method, depending on laboratory configuration. Measurements were performed on the same automated analyzer platform to ensure consistency. The urinary albumin-to-creatinine ratio (UACR) was calculated and expressed in mg/g.

Endothelial function was assessed by endothelium-dependent vasodilation (EnDV) and endothelium-independent vasodilation (EnIVD) according to the method of Celermajer. After a 12-hour overnight fast, measurements were performed using a Mindray M9 ultrasound system (5–12 MHz linear transducer, China) following standard protocols. EnDV and EnIVD were expressed as percentage change from baseline diameter. The brachial artery was imaged 2–10 cm above the antecubital fossa after 15 minutes of supine rest. Reactive hyperemia was induced by cuff inflation to 50 mmHg above systolic blood pressure for 5 minutes, followed by deflation, and the peak post-deflation diameter was recorded. After a 10-minute rest, EnIVD was assessed after administration of sublingual nitroglycerin (0.4 mg), with diameter recordings obtained for up to 15 minutes. Mean diameters were calculated from three cardiac cycles.

Serum concentrations of endothelin-1 (ET-1) and intercellular adhesion molecule-1 (ICAM-1) were measured as indicators of endothelial dysfunction. Fasting venous blood samples were centrifuged to obtain serum, aliquoted, and stored at −80°C until analysis. Quantitative determinations were performed using commercial immunoassay kits (Sera Care, USA) according to manufacturer instructions. Optical density was measured at 450 nm, and analyte concentrations were calculated from standard calibration curves. Results were expressed in fmol/mL for ET-1 and in ng/mL for ICAM-1.

Statistical analyses were performed using IBM SPSS Statistics version 21 (IBM, USA). Continuous variables are presented as mean ± standard deviation (M±SD), and categorical variables as number (percentage). Between-group comparisons of baseline characteristics were performed using the independent-samples t-test for normally distributed variables (or the Mann–Whitney U test for non-normal distributions) and the chi-square test or Fisher's exact test for categorical variables. To evaluate treatment-associated changes over time, within-group (pre- vs post-treatment) differences were analyzed using the paired-samples t-test (or Wilcoxon signed-rank test, as appropriate). Between-group differences in change over time were assessed by comparing Δ values (Δ=After−Before) using the independent-samples t-test (or Mann–Whitney U test). A two-sided p-value≤ 0.05 was considered statistically significant. Because treatment allocation was not randomized, we also performed adjusted analyses to account for potential baseline imbalances and confounding. Between-group differences in follow-up outcomes were assessed using ANCOVA (general linear models), with the baseline value of the respective outcome included as a covariate. Additional covariates included baseline LDL-cholesterol, systolic blood pressure, and eGFR. Adjusted results are reported where applicable.

The study was conducted in accordance with the principles of biomedical ethics and complied with the applicable national regulations of the Republic of Azerbaijan governing clinical research and the use of anonymized patient data. No experimental interventions beyond standard clinical practice were introduced.

The study adhered to the ethical principles outlined in the Declaration of Helsinki of the World Medical Association (2013 revision) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects developed by the Council for International Organizations of Medical Sciences (CIOMS).

All patient data were fully anonymized prior to analysis to ensure confidentiality and privacy protection. Written informed consent was obtained from all participants prior to inclusion in the study, allowing the use of their clinical and laboratory data for research purposes.

Table 1

Baseline demographic and clinical characteristics of the study groups

Parameter	Group 1 (n=27) M±SD	Group 2 (n=15) M±SD	p
Age (years)	52.3±5.8	51.6±6.2	0.64
Female, n (%)	12 (44.4)	8 (53.3)	–
Male, n (%)	15 (55.6)	7 (46.7)	–
BMI (kg/m²)	23.2±3.1	22.8±4.0	0.29
SBP (mm Hg)	132.1±5.7	134.4±6.1	0.21
DBP (mm Hg)	81.6±6.3	83.0±7.6	0.41
Total cholesterol (mg/dL)	184.2±41.6	181.9±47.8	0.71
Triglycerides (mg/dL)	170.4±37.9	162.1±40.8	0.48
LDL-cholesterol (mg/dL)	119.1±17.2	106.4±16.1	0.041
HDL-cholesterol (mg/dL)	56.5±8.0	59.4±7.7	0.19
Creatinine (mg/dL)	0.90±0.15	0.88±0.18	0.67
Serum albumin (g/dL)	2.92±0.18	2.81±0.17	0.06
eGFR (mL/min/1.73 m²)	92.3±3.6	92.0±3.8	0.78
Dapagliflozin, n (%)	13 (48.1)	–	–
Empagliflozin, n (%)	14 (51.9)	–	–

Results of the study and their discussion. The results showed that baseline demographic and clinical characteristics of the study participants were as follows. No statistically significant differences were observed between Group 1 and Group 2 with respect to age, body mass index (BMI), systolic blood pressure (SBP), or diastolic blood pressure (DBP) ($p>0.05$). The mean age of patients in Group 1 was

52.3±5.8 years, compared with 51.6±6.2 years in Group 2 (p=0.64). Lipid profile parameters were generally comparable between the two groups; however, low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in Group 1 than in Group 2 (p=0.041). Renal function parameters, including serum creatinine, estimated glomerular filtration rate (eGFR), and 24-hour proteinuria, did not differ significantly between the groups. In Group 1, 48.1% of patients received dapagliflozin, while 51.9% received empagliflozin. Baseline demographic and clinical characteristics of the study participants are presented in Table 1.

Over 6 months, patients receiving SGLT2 inhibitors showed greater improvement in endothelium-dependent vasodilation (EnDV) compared with standard therapy alone (between-group Δ, p=0.032). In contrast, endothelium-independent vasodilation (EnIVD) and carotid intima–media thickness (IMT) did not differ significantly between groups (p=0.521 and p=0.414, respectively).

A significantly larger reduction in albuminuria (UACR) was observed in the SGLT2 inhibitor group (p<0.001). Among circulating biomarkers, ET-1 and ICAM-1 declined more markedly with SGLT2 inhibitor therapy (both p<0.001 and p=0.002, respectively). hs-CRP also decreased, with a greater reduction in the SGLT2 inhibitor group (p=0.036). Longitudinal changes in endothelial function and circulating biomarkers are summarized in Table 2.

Table 2

Endothelial function and biomarker changes in membranous nephropathy patients treated with and without SGLT2 inhibitors

Parameter	Group 1, n=27 (M±SD)		Δ	Group 2, n=15 (M±SD)		Δ	P
	Before	After		Before	After		
EnDV (%)	9.8±2.7	11.2±3.2	+1.4	9.7±2.8	10.2±2.9	+0.5	0.032
EnIVD (%)	17.2±4.5	17.6±4.1	+0.4	16.8±3.9	16.5±3.8	−0.3	0.521
IMT (mm)	0.78±0.09	0.77±0.08	−0.01	0.74±0.07	0.74±0.08	0.00	0.414
UACR (mg/g)	437.3±60.2	112.0±48.5	−325.3	278.9±50.7	160.5±52.0	−118.4	<0.001
ET-1 (fmol/mL)	1.45±0.12	1.20±0.10	−0.25	1.07±0.10	1.06±0.09	−0.01	<0.001
hs-CRP (mg/L)	2.92±1.05	2.19±0.90	−0.73	2.75±0.88	2.28±0.88	−0.47	0.036
ICAM-1 (ng/mL)	378.4±24.7	215.8±23.0	−162.6	362.6±21.3	293.0±21.5	−69.6	0.002

Note: Δ indicates change over time (After − Before). P values represent between-group comparisons of Δ using the independent-samples t-test or Mann–Whitney U test, as appropriate. Abbreviations: EnDV, endothelium-dependent vasodilation; EnIVD, endothelium-independent vasodilation; IMT, intima–media thickness; UACR, urine albumin-to-creatinine ratio; ET-1, endothelin-1; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1.

To explore potential within-class heterogeneity, EnDV responses were compared between users of dapagliflozin and empagliflozin at baseline, after 6 months of follow-up, and for change from baseline. There was no significant baseline difference between subgroups (p=0.68). After 6 months, EnDV differed significantly between treatments (empagliflozin vs dapagliflozin, p=0.027), and the between-treatment difference in change from baseline remained significant after adjustment (p adj=0.036). Overall, these results suggest a more favorable EnDV profile with dapagliflozin than with empagliflozin at follow-up in this cohort.

This study has several limitations. It was observational, and treatment allocation was not randomized; therefore, residual confounding and selection bias cannot be excluded. Baseline differences between groups (e.g., LDL-cholesterol and albuminuria) may have influenced both treatment selection and subsequent outcomes. Although adjusted analyses were performed, unmeasured confounders may still remain. Larger randomized controlled trials are required to confirm these findings and clarify causal effects.

Primary membranous nephropathy is associated with endothelial impairment, and recent data indicate that vascular dysfunction may persist even after achieving remission. In the prospective cohort study of Prabhu, RR, et al (2025), patients with PLA2R-positive primary membranous nephropathy in remission after immunosuppressive therapy were evaluated and compared with healthy individuals. Endothelial function was assessed using flow-mediated and nitroglycerin-mediated vasodilation, as well as immunological markers of endothelial injury. The study population consisted predominantly of middle-aged adults with preserved renal function, low residual proteinuria, and normal serum albumin levels. Comparative analysis demonstrated no significant differences in vascular reactivity parameters or CD4+CD28null T-cell proportions between patients in remission and healthy controls. These findings suggest that in patients with primary membranous nephropathy who have achieved both clinical and serological remission, endothelial function is largely comparable to that observed in individuals without kidney disease [9].

In their review, Dou L et al. (2019) summarized the mechanisms underlying the toxic effects of high glucose/glucose breakdown products on the renal endothelium, including alterations in the synthesis of growth factors such as TGF-β and VEGF, induction of oxidative stress and inflammation, and decreased NO bioavailability. The authors presented potential treatments to reduce endothelial dysfunction in diabetic nephropathy. These data highlight the close relationship between the need for inhibitors (including SGLT2 inhibitors) in the treatment of nephropathies, which is consistent with our results [4].

Limitations. The study has several limitations, including a relatively small sample size and its single-center observational design, which may limit the generalizability of the findings. In addition, the non-randomized group allocation and relatively short follow-up period may have influenced the robustness of the observed associations.

Conclusion

Add-on sodium-glucose cotransporter 2 inhibitor therapy was associated with a greater improvement in endothelium-dependent vasodilation (p=0.032), a larger reduction in albuminuria (p<0.001), and more pronounced decreases in endothelin-1 (p<0.001), intercellular adhesion molecule-1 (p=0.002), and high-sensitivity C-reactive protein (p=0.036), while endothelium-independent vasodilation and intima–media thickness did not differ significantly between groups. Thus, in adult patients with idiopathic membranous nephropathy, add-on therapy with SGLT2 inhibitors was associated with a marked reduction in albuminuria and a significant improvement in circulating markers of endothelial dysfunction. A drug-level analysis demonstrated significant differences between dapagliflozin and empagliflozin after 6 months, with dapagliflozin showing a more favorable EnDV profile. These findings support potential endothelial and antiproteinuric benefits of SGLT2 inhibition in membranous nephropathy and warrant confirmation in larger randomized studies.

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Conflict of interest. The authors have no conflicts of interest to declare.

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