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CLINICAL AND GENETIC UNDERPINNINGS OF CARDIOVASCULAR COMPLICATIONS IN CHRONIC GLOMERULONEPHRITIS: MODERN APPROACHES TO THERAPEUTIC CORRECTION

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Introduction. Chronic glomerulonephritis (CGN) remains one of the most critical challenges in contemporary nephrology, closely tied to the high risk of developing end-stage renal disease (ESRD). However, clinical data indicates that the survival rate and long-term prognosis of CGN patients are predominantly dictated not by uremic progression alone, but by cardiovascular complications via the cardiorenal syndrome pathway. These events include left ventricular hypertrophy (LVH), refractory arterial hypertension (AH), accelerated atherosclerosis, and chronic heart failure (CHF).

The pathogenesis of cardiorenal damage in CGN is multifaceted, involving systemic immune-mediated inflammation, endothelial dysfunction, renin-angiotensin-aldosterone system (RAAS) overactivation, and alternative complement pathway dysregulation. Recent breakthroughs in molecular medicine suggest that phenotypic expressions of cardiovascular remodeling are strictly governed by specific genetic variants. Therefore, combining genetic stratification with modern targeted cardiorenal protective therapies represents the frontier of personalized nephro-cardiology.

Study Objective. To evaluate the clinical significance of EDN1, TNF, and CFH gene polymorphisms in the development of cardiovascular complications among CGN patients and to analyze the efficacy of modern cardiorenal-protective therapy using sodium-glucose cotransporter-2 (SGLT2) inhibitors and selective β-blockers.

Material and Methods. A comprehensive cohort study enrolled 120 patients (mean age 38.4±4.2 years) diagnosed with various clinical variants of CGN. Comprehensive laboratory workups assessed renal functional parameters, including serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) by CKD-EPI formula, and 24-hour proteinuria. Structural and functional cardiovascular profiles were meticulously characterized via Echocardiography (EchoCG) and 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

Venous blood samples were utilized for molecular-genetic screening. Genomic DNA was isolated, and genotyping was executed via Polymerase Chain Reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis for the following loci:

1. Endothelin-1 gene polymorphism: EDN1 (G-7244T);
2. Tumor Necrosis Factor-alpha gene polymorphism: TNF (G-7244T);
3. Complement Factor H gene polymorphism: CFH (rs1061170, C/T).

Patients were allocated into two parallel therapeutic cohorts:

- Group I (Control, n=60): Received standard background therapy consisting of conventional RAAS blockade (ACE inhibitors or Angiotensin Receptor Blockers - ARBs) along with symptomatic treatments.

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- Group II (Main, n=60): Received conventional therapy supplemented with a modern cardiorenal protector — SGLT2 inhibitor (Dapagliflozin, 10 mg/day) combined with a third-generation selective lipophilic β-blocker (Nebivolol, 5 mg/day).

All clinical, instrumental, and genetic datasets were statistically analyzed utilizing Statistica 10.0 software. Odds Ratios (OR), 95% Confidence Intervals (CI), and Chi-square (χ^2) tests were employed, with statistical significance established at $p < 0.05$.

Results and Discussion. Baseline genetic screening and subsequent risk-stratification unveiled a profound correlation between the studied polymorphisms and the severity of cardiorenal syndrome:

1. **EDN1 (G-7244T) Polymorphism:** Carrying the mutant T-allele and homozygous TT genotype of the EDN1 gene was heavily associated with severe, therapy-resistant forms of nephrogenic arterial hypertension (OR=2.65; 95% CI 1.34-5.23; p<0.01). This genetic variant upregulates endothelin-1 production, triggering persistent systemic vasoconstriction, microvascular damage, and increased arterial stiffness.

2. **TNF (G-7244T) Polymorphism:** Berrant variants of the TNF gene correlated with a sustained low-grade systemic inflammatory response, evidenced by elevated circulating proinflammatory cytokines. Patients harboring the mutant allele exhibited higher rates of cardiomegaly and diffuse myocardial fibrosis, expanding the risk of CHF development by 2.1-fold.

3. **CFH rs1061170 (C/T) Polymorphism:** The most striking results emerged from the analysis of the complement cascade regulator. Patients presenting with the homozygous **CC genotype** demonstrated hyperactivation of the alternative complement pathway, resulting in aggressive glomerular sclerosis and marked endothelial injury. The risk of developing severe left ventricular remodeling and diastolic dysfunction was significantly elevated in CC carriers compared to the wild-type TT genotype (OR=3.42; 95% CI 1.56-7.51; p<0.05).

Following a 6-month specialized treatment period, Group II (Dapagliflozin + Nebivolol) exhibited superior clinical outcomes over Group I:

Hemodynamic Stabilization: According to ABPM data, 48.3% of patients in Group II successfully achieved a physiological "Dipper" circadian blood pressure profile, restoring the necessary nocturnal blood pressure drop, compared to only 18.2% in Group I (p<0.05).

Myocardial Remodeling Reversal: EchoCG trends demonstrated a striking 15.4% reduction in Left Ventricular Mass Index (LVMI) among Group II participants (p<0.05), while Group I showed a negligible decrease of 5.1%. Dapagliflozin successfully countered the adverse mechanical and metabolic shifts induced by endothelin-1 hypersecretion.

Genotype-Specific Nephroprotection: 24-hour proteinuria dropped by 41.2% in Group II, and eGFR remained stable. Remarkably, even in patients burdened with the highest genetic risk profiles (**CFH CC** and **EDN1 TT** genotypes), the integration of SGLT2 inhibition managed to stabilize intrarenal hemodynamics and arrest the decline of glomerular filtration.

Conclusion. Cardiovascular complications in chronic glomerulonephritis are heavily dependent on molecular genetic predispositions. The EDN1 (T-allele), TNF

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(mutant variant), and CFH rs1061170 (CC genotype) stand out as potent, independent genetic predictors of adverse cardiorenal remodeling.

Relying solely on classic antihypertensive regimens is insufficient for high-risk CGN cohorts. Introducing SGLT2 inhibitors (Dapagliflozin) yields highly effective cardioprotective and nephroprotective benefits, directly overriding genetic resistance to standard therapies.

Early molecular screening targeting EDN1, TNF, and CFH loci allows clinicians to accurately forecast cardiovascular trajectories and transition from empirical treatments to highly individualized, genotype-guided preventive strategies.