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Comments on *"Effects of Dapagliflozin on miRNA Expression and Microalbuminuria in Diabetic Nephropathy"*

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Dear Editor,

I read with great interest the study by Yıldız Pehlivan et al. investigating the effects of dapagliflozin on micro-ribonucleic acid (miRNA) expression profiles and microalbuminuria in diabetic nephropathy (DN) patients. This study addresses a timely and clinically relevant question regarding the molecular mechanisms underlying sodium-glucose cotransporter-2 (SGLT-2) inhibitor-mediated renoprotection. While the findings contribute novel molecular data to the field, several methodological and interpretive considerations merit further discussion.

Methodological limitations: The retrospective single-arm design without a control group represents a fundamental limitation that warrants emphasis beyond the authors' own acknowledgment. The absence of a comparator cohort — either diabetic patients not receiving SGLT-2 inhibitors or those receiving alternative antidiabetic agents — makes it impossible to attribute the observed miRNA changes exclusively to dapagliflozin. This caveat is critical: miRNA expression is highly sensitive to glycemic fluctuations, and the substantial reduction in HbA1c (from 9.94% to 7.92%) observed in this study could independently account for the upregulation of miRNA-let7a, miRNA-25, and miRNA-130b, independent of any direct SGLT-2 inhibition effect (1). Without parallel groups, disentangling drug-specific molecular effects from glycemia-mediated changes remains methodologically unresolvable. Furthermore, the 60-day follow-up period, while sufficient to capture hemodynamic and glycemic responses, is arguably inadequate for evaluating epigenetic and miRNA-level adaptations in nephropathy. Renal fibrotic and inflammatory pathways, which these miRNAs are purported to regulate, evolve over months to years (5). The relatively small sample size (n=52), combined with non-normal data distribution requiring non-parametric testing, may have rendered the study underpowered to detect modest but clinically meaningful correlations between miRNA changes and microalbuminuria reduction.

The absent correlation: clinical significance: Perhaps the most provocative finding of this study is the lack of significant correlation between miRNA level changes and microalbuminuria reduction, despite both parameters improving significantly following dapagliflozin therapy. Beyond the authors' proposed explanations of limited sample size and follow-up duration, an alternative and clinically important interpretation merits consideration: microalbuminuria reduction by SGLT-2 inhibitors may operate primarily through hemodynamic mechanisms — specifically, reduction of intraglomerular pressure via tubuloglomerular feedback — rather than through miRNA-mediated molecular pathways [3]. Indeed, the role of tubuloglomerular feedback activation in mediating SGLT-2 inhibitor renoprotection has itself been subject to recent debate, particularly in patients with more advanced chronic kidney disease (CKD) (3). This would suggest that the observed miRNA upregulation represents a parallel, potentially independent molecular response to improved glycemic milieu, rather than

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a mechanistic mediator of albuminuria reduction. If confirmed in larger studies, this distinction would have important implications for the proposed utility of these miRNAs as biomarkers of dapagliflozin's renoprotective efficacy specifically, as opposed to glycemic control more broadly (1).

A nephrological perspective: From a clinical nephrology standpoint, the inclusion criteria of this study merit attention. Patients with a urinary albumin-to-creatinine ratio >30 mg/day for at least three months were classified as having DN; however, baseline serum creatinine values (mean 0.67 mg/dL) suggest a cohort with relatively preserved renal function. The renoprotective benefits of SGLT-2 inhibitors, as demonstrated in landmark trials such as DAPA-CKD and CREDENCE, are most pronounced in patients with more advanced CKD (eGFR 25–75 mL/min/1.73 m^2) [2,4]. Whether the miRNA expression patterns observed in early-stage DN are generalizable to patients with significant renal impairment — where the clinical stakes of biomarker identification are highest — remains an open and important question. Future studies stratifying patients by CKD stage and incorporating patients with overt proteinuria and reduced eGFR would substantially enhance the translational relevance of these molecular findings.

In conclusion, the study by Yıldız Pehlivan et al. makes a valuable contribution to our understanding of dapagliflozin's molecular effects in DN. Prospective, controlled, longer-term studies with adequate sample sizes and CKD-stage stratification are warranted to establish whether these miRNAs can serve as reliable, drug-specific biomarkers in clinical nephrology practice.

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