European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2025;31(1):1-10-.
https://doi.org/10.58600/eurjther2620

Original Research

Dapagliflozin Modulates MicroRNA Expression in Type 2 Diabetes Patients with Diabetic Nephropathy: A Retrospective Study

Deniz Yıldız Pehlivan[1], Hamit Yıldız[2], Gökhan Kaya[3]

[1] Department of Physiology, Graduate School of Health Sciences, İzmir Katip Çelebi University, İzmir, Türkiye
[2] Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
[3] Department of Internal Medicine, Ministry of Health, Pazarcik State Hospital, Kahramanmaraş, Türkiye

Received: 2024-10-07 **Accepted:** 2025-02-14 **Published Online:** 2025-02-28

Corresponding Author
Hamit Yıldız, Assoc.Prof.
Address: Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
E-mail: drhyildiz@hotmail.com

ABSTRACT

Objective: Diabetic nephropathy (DN) is one of the most serious microvascular complications of Diabetes Mellitus, the prevalence and mortality of which are increasing. Recently, microRNAs (miRNAs) used in the pathogenesis and diagnosis of many diseases have been identified. In this study investigate the relationship between albuminuria and miRNA levels in patients with type 2 diabetes mellitus (T2DM) treated with dapagliflozin, and to elucidate the potential nephroprotective effects of dapagliflozin through miRNA modulation.

Methods: This retrospective study included 47 T2DM patients (25 male, 22 female) with diabetic nephropathy (DN) treated with dapagliflozin. Blood samples were collected at baseline (day 0) and after approximately 60 days of treatment. Levels of miRNA-21, miRNA-141, and miRNA-377 were analyzed using real-time PCR. Clinical and laboratory parameters, including glucose, HbA1c, urine albumin and protein levels, were also assessed. Statistical analysis included the Wilcoxon signed-rank test and Spearman's rank correlation test.

Results: Significant decreases were observed in glucose, HbA1c, urinary protein, and albumin levels after dapagliflozin treatment ($p<0.01$). miRNA-21, miRNA-141, and miRNA-377 levels also decreased significantly following treatment ($p<0.01$). A positive correlation was found between day 0 miRNA-377 levels and day 0 serum glucose levels. A negative correlation was observed between day 0 miRNA-21 levels and day 60 HbA1c levels. No significant correlations were found between miRNA levels and urine albumin or protein levels.

Conclusion: Dapagliflozin treatment in T2DM patients with DN was associated with significant reductions in miRNA-21, miRNA-141, and miRNA-377 levels, alongside improvements in glycemic control and renal function markers. These findings suggest that dapagliflozin may exert its nephroprotective effects partly through modulation of DN-associated miRNAs. Dapagliflozin may be a therapeutic option to treat DN and may be an effective strategy to prevent kidney damage. Further research is warranted to elucidate the mechanisms underlying these effects and to explore the potential of miRNAs as biomarkers or therapeutic targets in DN management.

Keywords: Type 2 diabetes mellitus, dapagliflozin, microRNA, diabetic nephropathy, albuminuria

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from inadequate insulin secretion, diminished insulin action in peripheral tissues, or a combination of both. Chronic hyperglycemia causes functional and structural deterioration. It causes deterioration and irreversible damage to organs such as the retina, neurons, vascular structures and kidneys [1]. DN represents one of the most severe complications of DM and constitutes a significant cause of chronic kidney disease and end-stage renal failure [2].

Urinary albumin excretion serves as a critical parameter in the diagnosis of DN. Supportive diagnostic markers include cystatin C and creatinine. However, recent years have witnessed a quest for novel biomarkers capable of detecting early renal damage [3]. Contemporary research has focused on the association between miRNAs and chronic diseases, metabolic disorders, oncological conditions, and cardiovascular diseases [4]. Numerous miRNAs have been identified in relation to apoptosis and cellular differentiation, with clinical studies revealing data associated with alterations in miRNA expression [5].

Glucose reabsorption from the glomerular filtrate occurs in the proximal tubules via sodium-glucose cotransporters (SGLT-1 and SGLT-2). In healthy individuals, nearly all glucose is reclaimed into circulation, effectively clearing urine of glucose. Multiple therapeutic approaches are employed in DM management to maintain blood glucose levels within normal parameters. One such approach involves SGLT-2 inhibitors (SGLT-2i), which exert their antidiabetic effect by inhibiting glucose reabsorption in the proximal convoluted tubules. Beyond their plasma glycemic effects, SGLT-2i exhibit numerous systemic effects. They reduce blood pressure and body weight by augmenting fluid excretion through osmotic diuresis and natriuresis. Moreover, they are known to confer beneficial effects on cardiac and renal outcomes through various physiological mechanisms [6, 7]. SGLT2i's regulate renal glucose reabsorption by blocking SGLT2 cotransporters located in the proximal tubules, causing glycosuria and a decrease in intraglomerular pressure [8, 9]. The reduction in systemic blood pressure leads to decreased intraglomerular pressure. By modestly reducing the glomerular filtration rate, they also attenuate albuminuria. These renal protective effects, including the reduction of intraglomerular pressure and albuminuria, are independent of their glycemic effects. Another renal protective mechanism involves preventing glucose reabsorption in the tubules, thereby mitigating glucotoxicity and effectively preventing diabetic nephropathy [6, 7].

Main Points

DN represents one of the most severe microvascular complications of DM.

miRNAs are potent regulators of the genome.

Dapagliflozin, an SGLT-2 inhibitor, demonstrates efficacy in modulating DN-associated miRNAs and exhibits potential renoprotective properties.

miRNAs are small non-coding RNA molecules, approximately 22 nucleotides in length, involved in the regulation of post-translational gene expression [10]. Recent studies have elucidated that this novel class of non-coding RNAs participates in all biological processes, including cellular proliferation, apoptosis, and differentiation [11]. MiRNAs orchestrate the functioning of half of the human genome [12]. Recent years have witnessed a surge in studies investigating miRNAs associated with various pathological conditions [4]. Several investigations have explored miRNAs as potential biomarkers for DM [13-16]. Diabetes mellitus causes microvascular complications such as nephropathy, retinopathy and neuropathy. It has been reported that miRNAs affect angiogenesis, inflammation and apoptosis in the kidney, retina and peripheral neurons and play a very important role in the pathogenesis of microvascular complications. The role of miRNAs in the pathogenesis of diabetic microvascular complications has been investigated. According to the study results, miR-126, miR-29b and miR-125a appear to play a role in diabetes-related microvascular complications, while miR-146a has been shown to be linked to all these complications. On the other hand, it has been reported that vascular endothelial growth factors are the most affected miRNAs in diabetic microvascular problems [17] It has been shown that the miRNA profile is significantly altered in patients with diabetic nephropathy [18]. Dapagliflozin limits podocyte damage and protects against renal failure in DM [19]. There is no study on how miRNA 21, miRNA-141, and miRNA-377 levels change in patients diagnosed with DN and using dapagliflozin. In this context, our research is a first.

In this study, we evaluated the levels of miRNA-21, miRNA-141, and miRNA-377, as well as glucose, HbA1c values, urine albumin and protein levels in 47 patients diagnosed with DN and

treated with dapagliflozin. The objective of this investigation is to elucidate whether dapagliflozin exerts its nephroprotective effects through modulation of miRNA expression.

MATERIALS AND METHODS

Study Population

435 patients diagnosed with type 2 DM and followed at the Department of General Internal Medicine, Gaziantep University Faculty of Medicine, was evaluated for this study. Subjects receiving dapagliflozin therapy were selected from individuals adhering to routine DM management without comorbidities. This retrospective study designated the initiation of dapagliflozin treatment as day 0. Blood samples were obtained from 47 diabetic patients with DN (25 male, 22 female) during follow-up visits at approximately day 60 of dapagliflozin therapy. The collected specimens underwent appropriate processing, and the resultant plasma samples were preserved at -80°C. Patients aged 15-65 years were included in the study. Diabetic individuals with persistent albuminuria for at least three months were classified as having DN. The study compared data from day 0 and day 60 as two distinct groups. Patient demographics, biochemical parameters, complete blood count, hemoglobin A1c levels, urinalysis results, urine protein, urinary creatinine, and urine albumin levels were retrospectively extracted from medical records.

miRNA Isolation

miRNA extraction was performed using the PureLink® RNA Mini Kit. The purity and concentration of total miRNA obtained from each serum sample were determined using a NanoDrop 2000 Spectrophotometer.

cDNA Synthesis

Complementary DNA (cDNA) was synthesized from the extracted miRNA using components of the ID3EAL cDNA Synthesis kit according to the manufacturer's protocol. The resulting cDNA samples were stored at -20°C.

Real-Time PCR Analysis of miRNA

The synthesized cDNA was diluted 1:10. Amplification and detection of reference genes and target regions were accomplished using the ID3EAL miRNA qPCR System kit, following the manufacturer's instructions. miRNA expression levels were subsequently determined.

Statistical Analysis

The Kolmogorov-Smirnov test was employed to assess the normality of variable distributions. For non-normally distributed variables, comparisons between the two time points were conducted using the Wilcoxon signed-rank test. Correlations between numerical variables were analyzed using Spearman's rank correlation test. Statistical analyses were performed using SPSS for Windows version 22, with $p<0.05$ considered statistically significant.

RESULTS

The data obtained from the study are presented in the following tables.

Of the 47 patients included in the study, 25 (53.2%) were male and 22 (46.8%) were female. The mean age of these 47 patients is 54.09±8.48. The average body mass index of the participants was 25.74±0.40, the average systolic blood pressure was 124.38±2.56, and the average diastolic blood pressure was 75.11±2.71. The mean HOMA index of the study population was 3.81±0.9 and the mean diabetes disease duration was 2.60±1.01 (Table 1).

As presented in Table 2, analysis of laboratory findings in patients receiving dapagliflozin therapy revealed significant changes in glucose, creatinine, HbA1c ($p<0.01$), urinary protein, and urine albumin ($p<0.001$) levels.

Table 3 presents correlations between miRNA levels and glycemic parameters before and after dapagliflozin therapy. The data indicate a negative correlation between day 0 miRNA-21 levels and day 60 HbA1c levels. Conversely, a positive correlation was observed between day 0 miRNA-377 levels and day 0 serum glucose levels.

Table 4 illustrates the correlations between the examined miRNAs and urine albumin and protein levels.

As shown in Table 5, significant decreases in miRNA-21, miRNA-141, and miRNA-377 levels were observed on day 60 of dapagliflozin therapy ($p<0.01$).

Table 1. Averages of general and demographic characteristics

Introductory Features		n (%)	(Mean±SD)
Gender	**Male**	25 (%53.2)	
	Female	22 (%46.8)	
Age			54.09±8.48
Body mass index (kg/m²)			25.74±0.40
Systolic blood pressure (mmHg)			124.38±2.56
Diastolic blood pressure (mmHg)			75.11±2.71
Homa index			3.81±0.9
Duration of DM (year)			2.60±1.01

Table 2. Laboratory findings observed on days 0 and 60 of dapagliflozin therapy.

	Day 0 (Mean±SD)	Day 60 (Mean±SD)	p-value
Glucose (mg/dL)	224.42±105.63	151.34±40.94	**<0.01**
Creatinine (mg/dL)	0.67±0.15	0.75±0.14	**<0.01**
Sodium (mmol/L)	137.8±4.05	138.63±2.51	0.041
Potassium (mmol/L)	4.46±0.33	4.44±0.45	0.546
HbA1c (%)	9.85±1.83	7.84±1.37	**<0.01**
HDL (mg/dL)	47.70±9.02	49.32±7.72	0.843
Total cholesterol (mg/dL)	211.54±43.41	201.55±40.54	0.325
LDL (mg/dL)	141.34±33.36	129.17±27.50	0.007
Triglycerides (mg/dL)	207±100.2	191.42±83.53	0.143
Urinary creatinine (mg/dL)	110.64±50.13	86.53±41.62	0.033
Urinary protein (mg/dL)	23.73±29.27	14.69±22.97	**<0.001**
Urine albumin (mg/dL)	2.95±5.96	1.36±2.27	**<0.001**

Table 3. Correlations between miRNA levels and glycemic parameters on days 0 and 60 of dapagliflozin therapy.

	Glucose (Day 0)	Glucose (Day 60)	HbA1c (Day 0)	HbA1c (Day 60)
miRNA-21 (Day 0) p-value	0.842	0.912	0.912	0.007
miRNA-21 (Day 60) p-value	0.225	0.993	0.729	0.222
miRNA-141 (Day 0) p-value	0.768	0.700	0.407	0.467
miRNA-141 (Day 60) p-value	0.095	0.980	0.476	0.604
miRNA-377 (Day 0) p-value	0.001	0.346	0.113	0.327
miRNA-377 (Day 60) p-value	0.261	0.517	0.118	0.442

Table 4. Correlations between miRNAs and urine albumin and protein levels.

	Urine albumin (Day 0)	Urine albumin (Day 60)	Urine protein (Day 0)	Urine protein (Day 60)
miRNA-21 (Day 0) p-value	0.58	0.26	0.91	0.365
miRNA-21 (Day 60) p-value	0.618	0.956	0.983	0.409
miRNA-141 (Day 0) p-value	0.789	0.724	0.988	0.696
miRNA-141 (Day 60) p-value	0.006	0.097	0.217	0.345
miRNA-377 (Day 0) p-value	0.788	0.538	0.329	0.788
miRNA-377 (Day 60) p-value	0.208	0.579	0.378	0.491

Table 5. Changes in miRNA levels observed on days 0 and 60 of dapagliflozin therapy.

	Day 0 (Mean±SD)	Day 60 (Mean±SD)	p-value
miRNA-21	1.27±2.27	0.88±0.23	<0.01
miRNA-141	1.09±0.6	0.31±0.30	<0.01
miRNA-377	1.25±0.71	0.89±0.47	<0.01

DISCUSSION

Previous studies have shown that the levels of miRNA 21, miRNA 141, and miRNA 377 are altered in DN cases. In this study, we examined the effect of dapagliflozin on miRNAs associated with DN and found that there was a statistical decrease in miRNA 21, miRNA 141 and miRNA 377 levels on the 60th day after treatment. The pathogenesis of DN involves metabolic, hemodynamic, proinflammatory, and profibrotic factors. These factors can adversely affect the glomerular, tubular, interstitial, and arteriolar structures of nephrons. In the presence of various molecules, receptors, enzymes, and transcription factors, compensatory hypertrophy, extracellular matrix expansion, glomerulosclerosis, vascular hyalinosis, interstitial fibrosis, and tubular atrophy occur. Consequently, the deterioration of glomerular functions accelerates the progression to end-stage renal disease [20].

Studies conducted on patients diagnosed with type 2 DM have demonstrated that SGLT-2 inhibitors reduce glucose reabsorption from the proximal tubule, increase glucosuria, and significantly lower both HbA1c and serum glucose levels. It has also been observed that diabetic patients using these molecules experience a reduction in mortality associated with heart failure and chronic kidney disease [21, 22]. Subgroup analyses in scientific studies have shown that these agents reduce mortality in both diabetic and non-diabetic patients with heart failure. These findings support the hypothesis that the cardio-renal protective effect is mediated through mechanisms beyond renal glucose reabsorption. Okovityy et al. [23] reported that empagliflozin, an SGLT-2i, is a potential cardionephroprotector. Zhang et al. [19] showed that dapagliflozin significantly ameliorated dyslipidemia injury by suppressing renal podocyte pyroptosis both in vitro and in vivo. Dapagliflozin treatment has been reported to inhibit cell apoptosis, oxidative stress, and renal fibrosis [24].

Recent studies have revealed that numerous pathways are activated during the development of DN. miRNAs play a crucial role in regulating these pathways. In this study, we investigated the renal protective efficacy of dapagliflozin treatment and its relationship with miRNAs in patients with DN, a significant and potentially fatal complication of diabetes. Given that SGLT-2 inhibitors are known to positively influence the course of renal-related mortality and end-stage renal disease, we utilized serum samples from DN patients whose data were accessible in our clinic and whose blood samples were appropriately preserved.

miRNAs are single-stranded, non-coding RNA molecules consisting of approximately 22 nucleotides [10]. Recent data have shown that miRNAs are either up-regulated or down-regulated in various metabolic conditions and diseases [25, 26]. In this study, we examined changes in the levels of miRNA-21, miRNA-141, and miRNA-377, which have been found to be

elevated in experimental DN models. Our results revealed a statistically significant decrease in miRNA levels following dapagliflozin treatment. A positive correlation was observed between day 0 miRNA-377 levels and day 0 serum glucose levels. Our data demonstrated that both serum glucose and miRNA-377 levels were elevated prior to dapagliflozin treatment (day 0). Wang et al. [27] reported that high glucose concentrations led to up-regulation of miRNA-377 in cultured human and mouse mesangial cells. Another study found higher levels of certain miRNAs (miR-661, miR-571, miR-770-5p, miR-892b, and miR-1303) in patients with type 2 DM [28]. Wu et al. [29] discovered that exposure to high glucose levels increased miRNA-27a expression in glomerular mesangial cell cultures of diabetic rats. Conversely, some studies have reported decreased levels of miRNA-130b [30] and miRNA-137 [31] under high glucose conditions.

miRNA-21 is a miRNA associated with renal fibrosis. Animal model experimental studies show that miRNA-21 inhibitors support renal function [24]. Our results indicated a negative correlation between day 0 miRNA-21 levels and day 60 HbA1c levels. We observed that while both miRNA-21 and HbA1c levels were high before dapagliflozin treatment (day 0), they decreased significantly after treatment. A previous study demonstrated elevated levels of both miRNA-21 and HbA1c in patients with type 1 DM [32]. In a study in rats, dapagliflozin treatment caused a significant decrease in the expression of both miR-192 and miR-21 [24]. This study is the first to examine the effects of dapagliflozin on miRNA-21, miRNA-141, and miRNA-377 levels in humans.

Animal and in vitro studies have reported up-regulation of miRNA-21, miRNA-34a-5p, miRNA-141, miRNA-370, miRNA-503, miRNA-184, and miRNA-377 in DN cases [33]. miRNA-21 is a frequently studied multipotent miRNA. An in vitro and in vivo study demonstrated that over-expression of miR-21 inhibited proliferation of mesangial cells under high glucose conditions in DN mice. Additionally, it reduced the 24-hour urinary albumin excretion rate in diabetic mice and played a protective role in glomerular hypertrophy [34]. Kölling et al. [35] reported that miRNA-21 was among the most highly expressed miRNAs in the kidneys of mice with diabetes-induced kidney disease. They also found that in vitro and in vivo inhibition of miRNA-21 decreased mesangial expansion, interstitial fibrosis, macrophage infiltration, podocyte loss, albuminuria, and fibrotic and inflammatory gene expression. Another study demonstrated a correlation between miRNA-21 levels and the degree of glomerular fibrosis during kidney injury development. Over-expression of miRNA-21 enhanced TGF-β1-induced epithelial-mesenchymal transition. miRNA-21 inhibitors prevented the progression of epithelial-mesenchymal transition and renal fibrosis. Furthermore, they were reported to improve kidney structure and function in DN [35-37]. Numerous data support the role of miRNA-21 in DN cases. In this study, we observed a decrease in miRNA-21 levels after dapagliflozin treatment, suggesting that dapagliflozin may influence DN development and prognosis through miRNA-21.

miRNA-141 has been associated with cancer cell development and apoptosis. Following the identification of its relationship with apoptosis, the association between miRNA-141 and renal damage development in DN has been investigated. Study results support the relationship between increased miRNA-141 levels and renal pathological damage [38]. Li et al. [39] reported that miRNA-141 was up-regulated in the peripheral blood of DN patients, and this up-regulation significantly increased apoptosis and TNF-α and IL-6 expression. Additionally, miRNA-141 has been reported to be under-expressed in kidney tissue in DN models, and down-regulation of miRNA-141 has been shown to promote TGF-β1-induced renal scar formation [40, 41]. Wang et al. [40] reported that miRNA-141 could ameliorate renal fibrogenesis. Scientific data suggest that miRNA-141 may be effective in preventing DN-associated renal fibrosis. In this study, miRNA-141 levels decreased significantly after dapagliflozin treatment. Our data indicate that dapagliflozin may be effective in preventing DN progression.

The imbalance between oxidants and antioxidants in the body leads to oxidative stress, which causes inflammation and tissue damage. Fibronectin is a key matrix protein accumulated in excess in DN. Wang et al. [27] detected the presence of oxidative stress and inflammation in a DN study. miRNA-377 was found to be up-regulated in DN. miRNA-377 was reported to cause decreased expression of superoxide dismutase-1, superoxide dismutase-2, and PAK1, while over-expression of miR-377 alone increased oxidative stress and led to fibronectin accumulation in mesangial cells. Therefore, inhibition of miRNA-377 expression appears to be potentially effective in DN treatment. Studies have reported increased miRNA-377 levels in the urine [42] and body fluids [43] of diabetic kidney patients. Additionally, a significant positive correlation has been reported between miRNA-377 levels and HbA1c, ACR, and carotid intima-media thickness

[42]. Our study results revealed a decrease in miRNA-377 levels after dapagliflozin treatment. As miRNA-377 appears to play a role in DN, dapagliflozin has the potential to be an agent that could be used in DN treatment. We believe further studies are necessary in this context.

Limitations

The brevity of the study duration, limited patient cohort, and inability to measure oxidative stress markers constitute the primary limitations of this investigation. We posit that more comprehensive, randomized controlled trials comparing outcomes with a placebo group are necessary to corroborate the findings of the present study. Additionally, it would be beneficial to conduct prospective studies with different demographic characteristics or comorbid populations.

CONCLUSION

This study evaluated venous blood samples from 47 patients diagnosed with DN who had exhibited albuminuria for a minimum of three months. Blood samples were collected from patients receiving dapagliflozin treatment on day 0 (initiation of therapy) and day 60 post-treatment. Subsequent analyses compared pre-treatment levels of miRNA-21, miRNA-141, and miRNA-377 with post-treatment levels. A statistically significant reduction in the examined miRNA levels was observed in serum samples following treatment. Our findings suggest that dapagliflozin, an SGLT-2 inhibitor, possesses potential as a renoprotective agent, and that miRNA-21, miRNA-141, and miRNA-377 may play a role in modulating DN. In this context, Dapagliflozin may provide clinical benefits. miRNAs can be used both as biomarkers and potentially actionable targets in DN.

Conflict of interest: The authors declare no conflicts of interest.

Funding: This study was supported by Gaziantep University Scientific Research Projects with project number TF.UT.22.77.

Ethical Approval: This study was conducted with the ethics committee approval number 2022/315 from Gaziantep University Clinical Research Ethics Committee.

REFERENCES

[1] American Diabetes A (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care. 37:S81-90. https://doi.org/10.2337/dc14-S081.

[2] AKH Lim (2014) Diabetic nephropathy – Complications and treatment. Int J Nephrol Renovasc Dis. 7:361–381. https://doi.org/10.2147/IJNRD.S40172.

[3] K Simpson, A Wonnacott, DJ Fraser, T Bowen (2016) MicroRNAs in diabetic nephropathy: From biomarkers to therapy. Curr Diab Rep. 16:1–7. https://doi.org/10.1007/s11892-016-0724-8.

[4] VP Jayaseelan, P Arumugam (2020) Exosomal microRNAs as a promising theragnostic tool for essential hypertension. Hypertens Res. 43:74–75. https://doi.org/10.1038/s41440-019-0343-2.

[5] D. Sekar (2018) Comment on the potential role of microRNAs in hypertension. J Hum Hypertens. 32:639–640. https://doi.org/10.1038/s41371-018-0104-8.

[6] V Tsimihodimos, TD Filippatos, S Filippas-Ntekouan, M Elisaf (2017) Renoprotective effects of SGLT2 inhibitors: Beyond glucose reabsorption inhibition. Curr Vasc Pharmacol. 15:96–102. https://doi.org/10.2174/1570161114666161007163426.

[7] C Wanner, SE Inzucchi, JM Lachin, D Fitchett, M von Eynatten, M Mattheus, OE Johansen, HJ Woerle, UC Broedl, B Zinman (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 375:323–334. https://doi.org/10.1056/nejmoa1515920.

[8] A Lardaro, L Quarta, S Pagnotta, G Sodero, S Mariani, M Del Ben, G Desideri, E Ettorre, F Baratta (2024) Impact of sodium glucose cotransporter 2 inhibitors (SGLT2i) therapy on dementia and cognitive decline. Biomedicines. 12:1750. https://doi.org/10.3390/biomedicines12081750.

[9] K Kobayashi, M Toyoda, N Hatori, H Sakai, T Furuki, K Sato, Y Terauchi, K Tamura, A Kanamori (2022) Comparison of the blood pressure management between sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists. Sci Rep. 12:16106. https://doi.org/10.1038/s41598-022-20313-5.

[10] IG Albayrak (2022) miRNAs : Biogenesis, analysis methods and biomarker potential. Van Sag Bil Derg. 15:95–102. https://doi.org/https://doi.org/10.52976/vansaglik.952243.

[11] Q Cao, XM Chen, C Huang, CA Pollock (2019) MicroRNA as novel biomarkers and therapeutic targets in diabetic kidney disease: An update. FASEB Bioadv. 1:375–388. https://doi.org/10.1096/fba.2018-00064.

[12] DP Bartel (2009) MicroRNAs: Target recognition and regulatory functions. Cell. 136:215–233. https://doi.org/10.1016/j.cell.2009.01.002.

[13] LB Nielsen, C Wang, K Sørensen, CH Bang-Berthelsen, L Hansen, MLM Andersen, P Hougaard, A Juul, CY Zhang, F Pociot, HB Mortensen (2012) Circulating levels of MicroRNA from children with newly diagnosed type 1 diabetes and healthy controls: Evidence that miR-25 associates to residual beta-cell function and glycaemic control during disease progression. Exp Diabetes Res. 1–7. https://doi.org/10.1155/2012/896362.

[14] A Villard, L Marchand, C Thivolet, S Rome (2015) Diagnostic value of cell-free circulating micrornas for obesity and type 2 diabetes: A meta-analysis. J Mol Biomark Diagn. 6:1–21. https://doi.org/10.4172/2155-9929.1000251.

[15] Z Yang, H Chen, H Si, X Li, X Ding, Q Sheng, P Chen, H Zhang (2014) Serum miR-23a, a potential biomarker for diagnosis of pre-diabetes and type 2 diabetes. Acta Diabetol. 51:823–831. https://doi.org/10.1007/s00592-014-0617-8.

[16] C Zhao, J Dong, T Jiang, Z Shi, B Yu, Y Zhu, D Chen, J Xu, R Huo, J Dai, Y Xia, S Pan, Z Hu, J Sha (2011) Early second-trimester serum miRNA profiling predicts gestational diabetes mellitus. PLoS One. 6:e23925. https://doi.org/10.1371/journal.pone.0023925.

[17] A Ismail, HA El-Mahdy, MG Eldeib, AS Doghish (2023) miRNAs as cornerstones in diabetic microvascular complications. Mol Genet Metab. 138:1–11. https://doi.org/10.1016/j.ymgme.2022.106978.

[18] J Szostak, A Gorący, D Durys, P Dec, A Modrzejewski, A Pawlik (2023) The role of MicroRNA in the pathogenesis of diabetic nephropathy. Int J Mol Sci. 24:6214. https://doi.org/10.3390/ijms24076214.

[19] ZW Zhang, MQ Tang, W Liu, Y Song, MJ Gao, P Ni, DD Zhang, Q gui Mo, BQ Zhao (2024) Dapagliflozin prevents kidney podocytes pyroptosis via miR-155-5p/HO-1/NLRP3 axis modulation. Int Immunopharmacol. 131:111785. https://doi.org/10.1016/j.intimp.2024.111785.

[20] MK Sulaiman (2019) Diabetic nephropathy: Recent advances in pathophysiology and challenges in dietary management. Diabetol Metab Syndr. 11:1–5. https://doi.org/10.1186/s13098-019-0403-4.

[21] SD Wiviott, I Raz, MP Bonaca, O Mosenzon, ET Kato, A Cahn, MG Silverman, TA Zelniker, JF Kuder, SA Murphy, DL Bhatt, LA Leiter, DK McGuire, JPH. Wilding, CT Ruff, IAM Gause-Nilsson, M Fredriksson, PA Johansson, A-M Langkilde, MS Sabatine (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 380:347–357. https://doi.org/10.1056/nejmoa1812389.

[22] B Zinman, C Wanner, J Lachin, D Fitchett, E Bluhmki, S Hantel, M Mattheus, D Biomath, T Devins, OE Johansen, HJ Woerle, UC Broedl, SE Inzucchi (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 373:2117–2128. https://doi.org/10.1056/NEJMoa1504720.

[23] S Okovityy, D Ivkin, M Krasnova, A Karpov, G Ivanova, O Beresneva, E Kashine, Z Mikhail, O Galkina, M Parastaeva (2020) Can empagliflozin be a candidate for the role of a universal cardio- and nephroprotective drug in chronic heart failure without diabetes mellitus? Nephrology Dialysis Transplantation. 35:291. https://doi.org/10.1093/ndt/gfaa144.p0149.

[24] SM Al-Tantawy, SM Eraky, LA Eissa (2023) Promising renoprotective effect of gold nanoparticles and dapagliflozin in diabetic nephropathy via targeting miR-192 and miR-21. J Biochem Mol Toxicol. 37:e23430. https://doi.org/10.1002/jbt.23430.

[25] T Wang, H Zhu, S Yang, X Fei (2019) Let-7a-5p may participate in the pathogenesis of diabetic nephropathy through targeting HMGA2. Mol Med Rep. 19:4229–4237. https://doi.org/10.3892/mmr.2019.10057.

[26] S Deshpande, M Abdollahi, M Wang, L Lanting, M Kato, R Natarajan (2018) Reduced autophagy by a microRNA-mediated signaling cascade in diabacetes-induced renal glomerular hypertrophy. Sci Rep. 8:1–13. https://doi.org/10.1038/s41598-018-25295-x.

[27] Q Wang, Y Wang, AW Minto, J Wang, Q Shi, X Li, RJ Quigg (2008) MicroRNA-377 is up-regulated and can lead to increased fibronectin production in diabetic nephropathy. FASEB J. 22:4126–4135. https://doi.org/10.1096/fj.08-112326.

[28] C Wang, S Wan, T Yang, D Niu, A Zhang, C Yang, J Cai, J Wu, J Song, CY Zhang, C Zhang, J Wang (2016) Increased serum microRNAs are closely associated with the presence of microvascular complications in type 2 diabetes mellitus. Sci Rep. 6:1–9. https://doi.org/10.1038/srep20032.

[29] L Wu, Q Wang, F Guo, X Ma, H Ji, F Liu, Y Zhao, G Qin (2016) MicroRNA-27a induces mesangial cell injury by targeting of PPARγ, and its in vivo knockdown prevents progression of diabetic nephropathy. Scientific Reports. 6:1–12. https://doi.org/10.1038/srep26072.

[30] X Bai, J Geng, Z Zhou, J Tian, X Li (2016) MicroRNA-130b improves renal tubulointerstitial fibrosis via repression of Snail-induced epithelial-mesenchymal transition in diabetic nephropathy. Scientific Reports. 6:1–16. https://doi.org/10.1038/srep20475.

[31] F Han, S Wang, Y Chang, C Li, J Yang, Z Han, B Chang, B Sun, L Chen (2018) Triptolide prevents extracellular matrix accumulation in experimental diabetic kidney disease by targeting microRNA-137/Notch1 pathway. J Cell Physiol. 233:2225–2237. https://doi.org/10.1002/jcp.26092.

[32] M Fouad, I Salem, K Elhefnawy, N Raafat, A Faisal (2020) MicroRNA-21 as an early marker of nephropathy in patients with type 1 diabetes. Indian J Nephrol. 30:21–25. https://doi.org/10.4103/ijn.IJN.

[33] J Tang, D Yao, H Yan, X Chen, L Wang, H Zhan (2019) The role of microRNAs in the pathogenesis of diabetic nephropathy. Int J Endocrinol. 1:1–8. https://doi.org/10.1155/2019/8719060.

[34] Z Zhang, H Peng, J Chen, X Chen, F Han, X Xu, X He, N Yan (2009) MicroRNA-21 protects from mesangial cell proliferation induced by diabetic nephropathy in db/db mice. FEBS Lett. 583:2009–2014. https://doi.org/10.1016/j.febslet.2009.05.021.

[35] M Kölling, T Kaucsar, C Schauerte, A Hübner, A Dettling, JK Park, M Busch, X Wulff, M Meier, K Scherf, N Bukosza, G Szénási, M Godó, A Sharma, M Heuser, P Hamar, C Bang, H Haller, T Thum, JM Lorenzen (2017) Therapeutic miR-21 silencing ameliorates diabetic kidney disease in mice. Mol Ther. 25:165–180. https://doi.org/10.1016/j.ymthe.2016.08.001.

[36] X Xu, AJ Kriegel, Y Liu, K Usa, D Mladinov, H Liu, Y Fang, X Ding, M Liang (2012) Delayed ischemic preconditioning contributes to renal protection by upregulation of miR-21. Kidney Int. 82:1167–1175. https://doi.org/10.1038/ki.2012.241.

[37] J-Y Wang, Y-B Gao, N Zhang, D-W Zou, P Wang, Z-Y Zhu, J-Y Li, S-N Zhou, S-C Wang, Y-Y Wang, J-K Yang (2014) MiR-21 overexpression enhances TGF-β1-induced epithelial-to-mesenchymal transition by target smad7 and aggravates renal damage in diabetic nephropathy. Mol Cell Endocrinol. 392:163–172. https://doi.org/10.1016/j.mce.2014.05.018.

[38] T Sun, Y Liu, L Liu, F Ma (2020) MicroRNA-544 attenuates diabetic renal injury via suppressing glomerulosclerosis and inflammation by targeting FASN. Gene. 723:1–9. https://doi.org/10.1016/j.gene.2019.143986.

[39] Y Li, D Huang, L Zheng, H Cao, Z Fan (2019)Effect of microRNA-141 on the development of diabetic nephropathy through regulating AKT/AMPK signaling pathway by targeting insulin receptor substrate 2. J Cell Biochem. 120:8008–8015. https://doi.org/10.1002/jcb.28078.

[40] B Wang, P Koh, C Winbanks, MT Coughlan, A McClelland, A Watson, K Jandeleit-Dahm, WC Burns, MC Thomas, ME Cooper, P Kantharidis (2011) MiR-200a prevents renal fibrogenesis through repression of TGF-β2 expression. Diabetes. 60:280–287. https://doi.org/10.2337/db10-0892.

[41] M Xiong, L Jiang, Y Zhou, W Qiu, L Fang, R Tan, P Wen, J Yang (2012) The miR-200 family regulates TGF-β1-induced renal tubular epithelial to mesenchymal transition through Smad pathway by targeting ZEB1 and ZEB2 expression. Am J Physiol Renal Physiol. 302:369–379. https://doi.org/10.1152/ajprenal.00268.2011.

[42] MH El-Samahy, AA Adly, YI Elhenawy, EA Ismail, SA Pessar, MES Mowafy, MS Saad, HH Mohammed (2018) Urinary miRNA-377 and miRNA-216a as biomarkers of nephropathy and subclinical atherosclerotic risk in pediatric patients with type 1 diabetes. J Diabetes Complications. 32:185–192. https://doi.org/10.1016/j.jdiacomp.2017.10.014.

[43] Y Yang, L Xiao, J Li, YS Kanwar, F Liu, L Sun (2013) Urine miRNAs: Potential biomarkers for monitoring progression of early stages of diabetic nephropathy. Med Hypotheses. 81:274–278. https://doi.org/10.1016/j.mehy.2013.04.031.

How to Cite;

Yildiz Pehlivan D, Yildiz H, Kaya G (2025) The Dapagliflozin Modulates MicroRNA Expression in Type 2 Diabetes Patients with Diabetic Nephropathy: A Retrospective Study. Eur J Ther. 31(1):1-10. https://doi.org/10.58600/eurjther2520