

Functional Analysis of Solute Carrier Transporter Genes in the Pathogenesis of Diabetic Kidney Stones

Zahra Haq¹, Tahir Maqbool^{1*}, Mahwish Arooj³, Asya Ovais⁴, Sampana Fatima¹, Awais Altaf², Syed Usama Shayan Zaidi⁵, Muzammal Mateen Azhar², Sikander Hayat², Shabana Akhtar⁶

¹ Department of Physiology, Shahida Islam Medical and Dental College, Lodhran

² Department of IMBB (Institute of Molecular Biology and Biotechnology), University of Lahore

³ University College of Medicine and Dentistry, University of Lahore, Lahore, Pakistan

⁴ Department of Physiology, Quaid-e-Azam Medical College, Bahawalpur

⁵ Department of Physiology, Queen Mary College, Lahore

⁶ Scholar School System, Bradford Campus

ABSTRACT

Background: Nephrolithiasis is an under-recognized yet clinically significant complication in patients with type 2 diabetes mellitus (T2DM). Increasing evidence suggests that dysfunction of renal solute carrier (SLC) transporters contributes to lithogenic urinary alterations. This study investigates the expression and functional relevance of key SLC transporters in diabetic nephrolithiasis. **Objective:** To evaluate the gene expression and protein levels of SLC26A1, SLC26A6, and SLC22A4 in T2DM patients with nephrolithiasis and determine their role in disease pathogenesis. **Methods:** A retrospective case-control study was conducted on 80 individuals, comprising 20 healthy controls, 20 patients with T2DM, 20 with nephrolithiasis, and 20 with diabetes and nephrolithiasis. Clinical, biochemical, and hematological parameters were recorded. Protein quantification was performed using ELISA, and gene expression of SLC26A1, SLC26A6, and SLC22A4 was assessed via RT-PCR. Statistical analysis was conducted using SPSS 26.0. **Results:** T2DM nephrolithiasis patients exhibited significantly elevated HbA1c levels (mean ~9%) and poor glycemic control, especially among females. Renal function tests showed elevated serum urea, creatinine, and uric acid. Expression of SLC26A1, SLC26A6, and SLC22A4 was markedly reduced in diseased patients compared to controls ($p < 0.05$). Protein quantification confirmed significantly lower transporter concentrations in affected individuals. These molecular alterations correlated with biochemical markers of renal impairment and systemic inflammation. **Conclusion:** Reduced expression and activity of SLC26A1, SLC26A6, and SLC22A4 contribute to the pathophysiology of nephrolithiasis in T2DM. These transporters may serve as potential biomarkers and therapeutic targets. Molecular profiling of transporter dysfunction offers promising avenues for early diagnosis and personalized treatment of diabetic stone formers.

Keywords: Type 2 Diabetes Mellitus, Nephrolithiasis, Solute Carrier Transporters, SLC26A1, SLC26A6, SLC22A4, Gene Expression, Oxalate Metabolism.

INTRODUCTION

Today, more than 600 million people worldwide are affected by type 2 diabetes mellitus (T2DM), and numbers continue to climb, fueled by demographic shifts and lifestyle changes. Nephrolithiasis, an under-appreciated but clinically significant comorbidity in diabetes, is a condition whose macrovascular and microvascular complications, especially cardiovascular disease, retinopathy, neuropathy, and classical diabetic nephropathy, are well recognized [1]. Epidemiological studies indicate that patients with T2DM are at a two to threefold increased risk of kidney stone formation, and the prevailing crystalline species is calcium oxalate. In addition to acute, severe renal colic and frequent recurrent urinary tract infections, stones accelerate the decline of renal function and enhance the disease burden of diabetic kidney disease, increasing progression to end-stage renal failure [2]. The solute carrier (SLC) transporter superfamily is a large family of membrane proteins, estimated to comprise more than 400 genes in over 60 families, that is at the heart of renal solute homeostasis [3]. SLC transporters expressed along every segment of the nephron govern the reabsorption and secretion of key solutes, ions, organic metabolites, and xenobiotics, to regulate urinary concentrations below the threshold for crystallization. Among these are critical anion exchangers, SLC26 anion exchangers (SLC26A1, SLC26A6), and SLC13A2 (NaDC1) that mediate oxalate and citrate flux, respectively. Sculpture of the urinary milieu to prevent stone

formation is further accomplished by complementary activities of sodium-glucose cotransporters (SGLTs), sodium-phosphate cotransporters (NaPi-IIa/IIc), calcium channels (TRPV5), and sodium exchangers (NHE3, NKCC2) [4]; [5]. In T2DM, chronic hyperglycemia, oxidative stress, and low-grade inflammation work in concert to perturb this finely tuned transport network. Non-enzymatic glycation of glucose excess fosters the generation of advanced glycation end products, activation of NADPH oxidases, and breakdown of protein stability and function via excess glucose. Epigenetic reprogramming of transporter gene expression is elicited by inflammatory cytokines and dysregulated microRNAs. The mislocalization, downregulation, and functional impairment of SLC proteins lead to a disruption of solute handling and urinary supersaturation for crystal nucleation [6]; [7]. Also, diabetes is accompanied by a potent inhibitor of calcium crystal aggregation, citrate, which is also compromised. While hyperglycemia-induced oxidative modifications of key thiol residues and inflammatory transcriptional changes impair NaDC1 transport activity and lead to hypocitraturia, NaDC1 on proximal tubular cells reclaims filtered citrate [8]. Solute transport and the interplay with glycemic control are exemplified by glucose reabsorption via SGLT2 (SLC5A2). SGLT2 inhibitors (canagliflozin, dapagliflozin) provide glucosuric and cardiovascular benefits but also cause osmotic diuresis and affect

proximal sodium and calcium handling with possible stone risk. Cryo-EM structures of SGLT2 bound to inhibitors have recently provided molecular insights into the mechanisms of blockade that can be exploited to develop such agents for dual glycaemic and lithogenic modulation [9, 10]. Although there is increasing mechanistic evidence, transporter gene variant analysis and protein expression in diabetic stone formers have not been systematically studied. In this study, we investigate SLC26A1 and SLC26A6 common and rare variants as well as quantify OCTN1 (SLC22A4) levels in renal tubular epithelium in T2DM patients, with and without calcium oxalate nephrolithiasis. The Current aimed to decipher the role of solute carrier transporter dysfunction in nephrolithiasis pathogenesis and to identify biomarkers and therapeutic targets for the prevention and management of nephrolithiasis in diabetes mellitus [11].

MATERIALS AND METHODS

Study Design

This retrospective case control investigation enrolled participants from Bahawal Victoria Hospital, Bahawalpur, and the University of Lahore after approval from the University of Lahore, Lahore, Pakistan. Four study groups were defined: one healthy control group and three groups of type 2 diabetes mellitus (T2DM) patients. D1 comprised T2DM patients without additional comorbidities; D2 included nephrolithiasis patients without additional comorbidities; D3 comprised T2DM patients with nephrolithiasis; and D4 consisted of healthy controls. This stratification enabled a comprehensive assessment of oxalate and ion transport dynamics across progressive diabetic complications.

Inclusion and Exclusion Criteria

Eligibility was based on a detailed review of medical histories, family records, and clinical examinations. Men and women aged 20 years and above were considered. The control group consisted of healthy adults, often acquaintances of diabetic patients with no history of diabetes, hypertension, IHD, or stroke, confirmed by glycated hemoglobin (HbA1c) < 6.5% and blood pressure < 120/80 mmHg. Diabetic groups were included according to documented diagnoses. Exclusion criteria encompassed pregnant or lactating women, individuals with malignancies, and patients with advanced or end-stage renal disease.

Collection of Demographic and Clinical Data

Demographic variables and clinical profiles were recorded for every participant. Trained medical personnel conducted physical examinations within both the inpatient wards and outpatient clinics of the Department of Medicine, ensuring representative sampling across the hospital population.

Sample Size

Calculation of sample size was done according to Gao *et al.*, [12]. A total of 80 subjects, 20 in each group, were enrolled in the current study. 20 healthy controls, 20 diabetics with no complications, 20 patients with kidney stones with no complications, and 20 diabetic subjects with nephrolithiasis were selected for the study.

Sample Collection

Five milliliters of venous blood were drawn aseptically via standard venipuncture. Samples were partitioned equally into an EDTA-

anticoagulated tube and a plain tube. Specimens were transported under cold-chain conditions to the Institute of Molecular Biology and Biotechnology (IMBB), University of Lahore. Serum tubes were centrifuged at 3000 rpm for 10–15 minutes (Sigma 3-30k); plasma was aliquoted and stored at –20 °C for subsequent assays. EDTA tubes were reserved for genomic DNA isolation.

Anthropometric Measurements

Body weight and stature were measured with calibrated scales and stadiometers, and body mass index (BMI) was calculated as weight (kg) / height² (m²) according to the standard formula as described by Bhupathiraju *et al.* [13] stated below:

$$[BMI = \text{weight (kg)} / [\text{height (m)}]^2]$$

Biochemical Estimations

Fasting plasma glucose was quantified via the glucose oxidase (GLU-OX) method. HbA1c levels were determined by a latex agglutination assay (GLYCOHEMOGLOBIN A1c kit, DIRUI, Changchun, China). Serum urea (blood urea nitrogen, BUN) and creatinine were measured using combined renal function kits.

Enzyme-Linked Immunosorbent Assay

Serum samples were added to microplate wells containing specific antibodies. Incubation is done to allow protein binding. Unbound components were washed off. An enzyme-linked protein-specific detection antibody was added, followed by a chromogenic substrate. Protein levels were quantified by spectrophotometric measurement of colour change.

DNA Extraction

Genomic DNA was extracted from EDTA-anticoagulated blood using the QIAamp DNA Mini Kit (Qiagen; Batch 166030545; Briogene Pvt. Ltd., Hilden, Germany) according to the manufacturer's protocol. DNA extraction was performed on 5 mL of anticoagulated whole blood, which was then stored at 20°C. The method was also applied to 50 µL of the entire blood spotted on the Whatman filter paper. After drying, the spot was fixed with methanol and stored at room temperature. A disc five millimeters in diameter was punched out and mixed with 100 µL of deionized sterile water and placed in a boiling water bath for 30 minutes to lyse the cells. We used 20 µL of this mixture as a DNA source for amplification.

DNA Quantification

DNA concentration was measured by the Nanodrop spectrophotometer [14]. Absorbance was recorded as 260 nm (50 µg/ml of dsDNA). The ratio of absorbencies at 260 nm and 280 nm was taken as 1.8 with a pure sample. A ratio less than 1.8 indicated that the preparation is contaminated with phenol or protein.

Polymerase Chain Reaction (PCR) Amplification

Conventional PCR was performed with 100 ng purified genomic DNA, 0.5 µM of

APOE P1 and APOE P2 primers; P1 Forward sense (5' AACAACTGACCCCGGTGGCG 3'), and P2 Antisense (5' ATGGCGCTGAGGCCGCGCTC 3'), and P3 forward sense

5'CCCACCTGCGCAAGCT 3'.

The reaction mixture contained (200 µM of dNTP mixture, 1 M betaine, 2mM MgCl₂, 2.5 U Taq DNA polymerase (BioQuest), and reaction buffer in a 50-µl reaction volume.

Each PCR reaction mixture comprised of 100ng (almost 2 μ L) of DNA, 0.8 μ L of both primers (10 pmol/ μ L each), 8 μ L master mix and 5 μ L of distilled water.

Following steps were performed: The amplification was initiated at 95°C for 2 minutes, followed by 45 cycles of 95°C for 30 seconds, 68°C for 30 seconds, and 72°C for 30 seconds, and then a final extension at 72°C for 7 minutes.

Statistical Analysis

Analyses were conducted using SPSS version 26.0. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as frequency and percentage. One-way analysis of variance (ANOVA) assessed within-group differences; two-way ANOVA compared between groups. A p-value $\leq$ 0.05 denotes statistical significance. All data underwent rigorous quality checks for completeness and integrity before analysis.

Results

The study was conducted on 80 individuals, 40 healthy controls and 40 diseases aged between 25 to 60 years. 41 study subjects (51.2%) were males, and 39 of them (48.8%) were females.

Almost all of the individuals belonged to the Bahawalpur Division or its nearby areas. 17 people (21.3%) were from an urban area, and the remaining 63 (78.8%) were from a rural area. Family history of diabetes was positive in 8 males, who constituted 10 % of the total study subjects, and in 11 females, who constituted about 78.8% of the total study subjects.

16 of the males were smokers, who were 20 % of all study subjects. None of the females was a smoker. None of the study subjects was addicted to alcohol, as shown in Table 1.

Table 1: Demographic and Clinical Factors of Study Subjects

Variables	Characteristics
Total Subjects	80
Age	25 to 60
Gender	Males 41 (51.2%), Females 39 (48.8%)
Region	Bahawalpur and Its Surrounding Areas
Urban	17 (21.3%)
Rural	63 (78.8%)
Family History of Diabetes	Positive in Males: 8 (10%), Positive in Females: 11 (13.7%) = 23.7%
Family History of Kidney Stones	Positive in Males: 13 (16.2%), Positive in Females: 08 (10%) = 21 (26.2%)
Smoking	16 (20% of All Subjects), All Males
Alcohol	Nil

Table 2 presents the main parameters obtained from the CBC (Complete Blood Count) reports of diabetic patients with nephrolithiasis. Overall, reduced hemoglobin levels were observed in the study group. White blood cell counts showed a tendency toward

elevation, indicating possible ongoing infections among these patients.

Platelet counts remained within the normal reference range, reflecting a relatively stable blood clotting profile.

Table 2: Baseline CBC Profile of Nephrolithiasis Diabetic Patients

Blood Parameters	(Mean $\pm$ SD)	
	Control	Patients
Hemoglobin (g/dL)	12.1 $\pm$ 0.5	10.8 $\pm$ 1.87
White Blood Cell (cells/ μ L)	3.11 $\pm$ 0.22	7.3 $\pm$ 0.11
Platelet Count (cells/ml)	500 $\pm$ 100.1	310 $\pm$ 10.2

Serum Electrolytes Analysis

The electrolytes in the serum of the patients were assessed, and the results indicated a mean sodium ion concentration of 140.18 $\pm$ 2.52 mmol/L. Mean potassium ion concentration was 3.95 $\pm$ 0.31 mmol/L.

Concentration of chloride ions was 101.63 $\pm$ 3.41 mmol/L and bicarbonate ion concentration was 23.54 $\pm$ 3.47 mmol/L. Variation in electrolyte concentrations indicated defects at carrier levels in nephrons of patients with kidney stone disease, as shown in Table 3.

Table 3: Analysis of Serum Electrolytes

Parameters	Mean $\pm$ SD	
Sodium (mmol/L)	140 $\pm$ 10.5	140.18 $\pm$ 2.52
Potassium (mmol/L)	4.2 $\pm$ 0.1	3.95 $\pm$ 0.31
Chloride (mmol/L)	103 $\pm$ 0.2	101.63 $\pm$ 3.41
Bicarbonate (mmol/L)	25 $\pm$ 5.01	23.54 $\pm$ 3.47

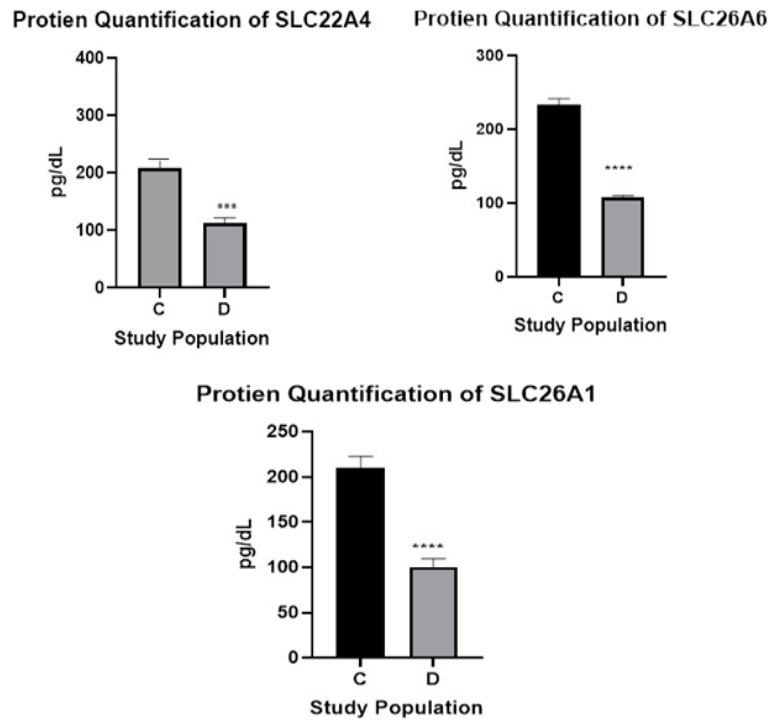
Random blood sugar (RBS) levels were assessed to evaluate the glycemic status of diabetic patients with nephrolithiasis. A comparative analysis revealed higher RBS levels in female patients than in males. For diagnostic confirmation, fasting blood glucose and glycated hemoglobin (HbA1c) values were also evaluated, both of which were markedly elevated in the patient group compared to healthy controls as shown in table 4.

Protein Expression of SLC26A1, SLC6A6 and SLC22A4

Protein quantification of SLC26A1, SLC2A6, and SLC22A4 revealed a significant reduction in expression among nephrolithiasis patients compared to healthy controls. As illustrated in Figure 1, protein concentrations were notably lower in the diseased group, with statistical analysis confirming a significant difference between the two populations.

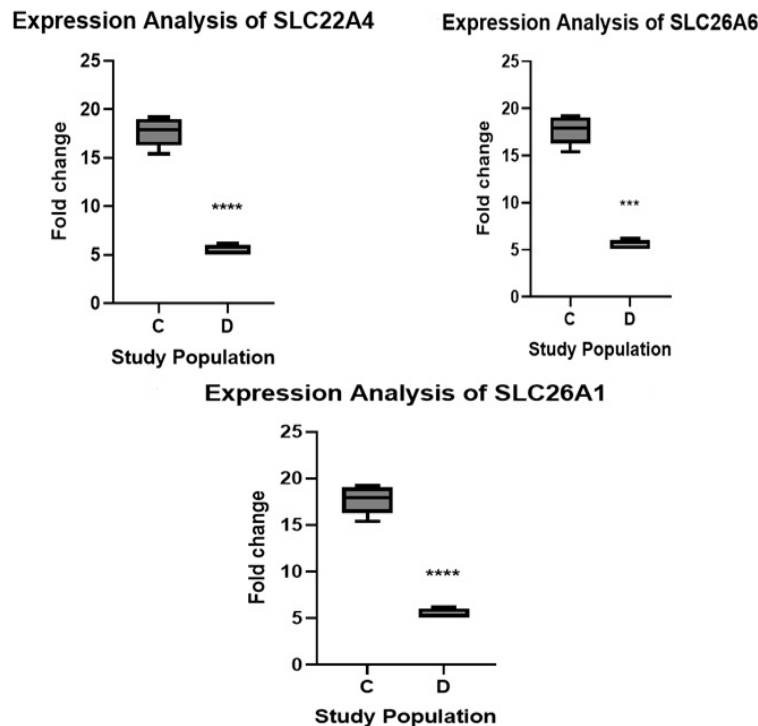
Table 4: Distribution of Biochemical Parameters related to Diabetes

Variables	Controls	Diabetic
Blood Sugar Fasting	<115 mg/dL	135-385mg/dL
Glycated Hemoglobin (HbA1c)	<5.0%	6.5 to12.8

**FIGURE 1:** Protein Quantification of SLC26A1, SLC26A6 was also Done. Where C is Control and D is the Nephrolithiasis Group. *** Indicates a Significant Difference between the Groups.**Gene Expression Analysis of SLC26A1, SLC26A6 and SLC22A4**

Gene expression analysis of SLC26A1, SLC26A6 and SLC22A4 were further performed. Results of gene expression depicted a lower level of

all these genes in the nephrolithiasis group while in the control group their level was increased. The p-value also demonstrated significance, as shown in fig 2.

**FIGURE 2:** The Figure Depicts Gene Expression Analysis of SLC26A1, SLC26A6, and SLC22A4 Genes. The Genes are Expressed in Diabetic Nephrolithiasis Patients to a Lesser Extent than in Healthy Controls. Where **** Indicates a Significant difference between the Groups.

Discussion

The demographic analysis of the study population, comprising 80 participants with an equal distribution of 40 diseased and 40 control individuals, provided important contextual insight into the background characteristics influencing disease development. A slightly higher proportion of males (51.2%) compared to females (48.8%) was noted, with the majority of participants (78.8%) residing in rural areas of the Bahawalpur Division. This rural predominance may reflect socioeconomic limitations and healthcare access disparities that could contribute to diagnosis and delayed management of chronic conditions like diabetes and nephrolithiasis. Family history patterns revealed that 23.7% of the subjects had a family history of diabetes mellitus, and 26.2% had a familial background of kidney stones, suggesting a potential genetic predisposition within the study population. Lifestyle data showed that 20% of the male participants were smokers, while alcohol consumption was absent in all subjects, indicating minimal confounding from alcohol-related nephrotoxicity [15, 16]; [17];[18]. Hematological parameters demonstrated subtle yet significant abnormalities among nephrolithiasis diabetic patients. The mean hemoglobin level was 10.8 ± 1.87 g/dL, indicating mild anemia likely due to chronic inflammation or early renal insufficiency. The white blood cell count, averaging 7.3 cells/ μ L, remained within the normal reference range but indicated an inflammatory tendency in some individuals, corroborated by the disease pathology. Platelet count was within normal limits (mean 310/ml), suggesting no overt hematologic dyscrasia but reflecting a preserved coagulation profile in the cohort. These findings support the presence of a low-grade inflammatory milieu, a known driver of both diabetic complications and renal crystal pathogenesis. Serum electrolyte analysis further illustrated the renal involvement in these patients. Sodium, potassium, chloride, and bicarbonate levels, while largely within physiological range, showed slight deviations. The mean serum sodium level was 140.18 ± 2.52 mmol/l and potassium 3.95 ± 0.31 mmol/l, which may suggest subtle proximal tubular dysfunction affecting ion reabsorption. Bicarbonate levels were mildly decreased (23.54 ± 3.47 mmol/l), suggesting subclinical metabolic acidosis, a known risk factor for calcium oxalate stone formation. These variations point toward transporter-level impairments within the nephron, particularly involving the solute carrier families responsible for ionic equilibrium, such as SLC4A4 (bicarbonate transport) and SLC26A1/A6 (anion exchange). Renal function tests yielded evidence of mild to moderate renal dysfunction. The mean serum urea level was elevated at 37.36 ± 19.65 mg/dL, and blood urea nitrogen (BUN) was 20.56 ± 5.21 mg/dL. Serum creatinine, with a mean of 1.43 ± 1.04 mg/dL, indicated impaired glomerular filtration in some patients, although still within early stages of chronic kidney disease for most. Uric acid levels were moderately raised (mean 6.65 ± 1.15 mg/dL), contributing to a lithogenic urinary environment and suggesting the likelihood of mixed calcium oxalate and uric acid stone formation. These findings validate the presence of biochemical alterations consistent with both diabetic nephropathy and nephrolithiasis. Glycemic control analysis painted a concerning picture of poor metabolic management, particularly in female patients. Random blood sugar levels were higher in females (approximately 300 mg/dL) than in males (approximately 250 mg/dL), and HbA1c levels mirrored this trend, with females averaging about 9% compared to 7% in males. These observations underscore gender-specific vulnerability to poor glycemic regulation

and its sequelae, particularly in terms of glycation-mediated transporter dysfunction, oxidative stress, and microvascular damage all of which contribute to nephrolithiasis pathogenesis in diabetes. Biochemical comparisons between diabetic and control groups confirmed significant differences. Diabetic individuals had fasting blood glucose levels ranging from 135 to 385 mg/dL and HbA1c levels from 6.5% to 12.8%, far exceeding control group values of <126 mg/dL and <5.7%, respectively. This hyperglycemic state is a key initiator of advanced glycation end products and reactive oxygen species generation, which directly impact SLC transporter protein structure and function, leading to solute imbalance and promoting crystallization. However, most of the studies largely focused on epidemiological data, our investigation goes further to establish a molecular explanation for this clinical observation. We found that the expression and protein levels of SLC26A1 and SLC26A6, critical anion exchangers responsible for oxalate handling, were significantly diminished in diabetic stone formers, suggesting a primary transporter defect contributing to systemic oxalate accumulation and urinary supersaturation [1]. These results align with and extend upon prior findings by Schumann et al. [1], Gee et al. [6], Yang et al. [4], and Zhang et al. [2], who reported that patients with T2DM exhibit a two- to three-fold higher risk of kidney stone formation compared to non-diabetic individuals, with calcium oxalate being the predominant stone composition [19, 20]. Molecular assessments of gene expression and protein quantification presented compelling evidence supporting transporter dysfunction as a pivotal mechanism in diabetic nephrolithiasis. Real-time PCR results revealed significantly reduced gene expression of SLC26A1, SLC26A6, and SLC22A4 in diseased individuals compared to healthy controls. Corresponding protein quantification via ELISA demonstrated markedly lower levels in patients: SLC26A1 was reduced to 100 pc/dL (versus 200 pc/dL in controls), SLC26A6 to 100 pg/dL (versus 230 pg/dL), and SLC22A4 to 110 pc/dL (versus 200 pg/dL). These reductions are indicative of transcriptional and post-transcriptional suppression of key transporters responsible for oxalate, sulfate, and carnitine handling. The downregulation of SLC26A6 compromises oxalate secretion into the urine, increasing systemic oxalate load and calcium oxalate crystal nucleation. Similarly, defective SLC26A1 impairs basolateral oxalate clearance, further elevating intracellular and urinary oxalate. SLC22A4, which transports carnitine, may influence oxidative stress by modulating mitochondrial function and fatty acid metabolism; its deficiency may exacerbate renal injury and stone formation through increased reactive oxygen species [21]. The collective interpretation of these findings supports a multifactorial model of diabetic nephrolithiasis pathogenesis. It incorporates demographic and lifestyle influences, glycemic dysregulation, biochemical imbalances, renal impairment, and transporter gene dysfunction. The convergence of reduced transporter gene expression and protein levels with biochemical disturbances in diabetics afflicted by kidney stones highlights these transporters particularly SLC26A1, SLC26A6, and SLC22A4, as both mechanistic contributors and potential therapeutic targets associated with previous study [22]. The evidence strongly advocates for future research aimed at restoring transporter function to correct urinary solute profiles and prevent renal stone formation in diabetic individuals.

Conclusion

This study establishes a clear association between reduced expression and protein levels of key solute carrier transporters

SLC26A1, SLC26A6, and SLC22A4 and the pathogenesis of nephrolithiasis in patients with type 2 diabetes mellitus. The findings suggest that diabetic metabolic disturbances, particularly chronic hyperglycemia and oxidative stress, contribute to transport dysfunction, leading to urinary supersaturation with lithogenic solutes such as oxalate and calcium, thereby promoting renal stone formation.

These results underscore the molecular basis of diabetic nephrolithiasis and highlight the potential of these transporter genes as biomarkers for early risk prediction and as therapeutic targets for precision-based management. Further longitudinal and mechanistic studies are warranted to validate these findings and facilitate the development of transporter-directed preventive and therapeutic strategies in diabetic kidney stone formers.

REFERENCES

- [1] T. Schumann *et al.*, "Solute Carrier Transporters as Potential Targets for the Treatment of Metabolic Disease," *Pharmacological Reviews*, vol. 72, no. 1, pp. 343-379, 2020, doi: 10.1124/pr.118.015735.
- [2] Y. Zhang, Y. Zhang, K. Sun, Z. Meng, and L. Chen, "The SLC transporter in nutrient and metabolic sensing, regulation, and drug development," (in eng), *J Mol Cell Biol*, vol. 11, no. 1, pp. 1-13, Jan 1 2019, doi: 10.1093/jmcb/mjy052.
- [3] J. Le, Y. Chen, W. Yang, L. Chen, and J. Ye, "Metabolic basis of solute carrier transporters in treatment of type 2 diabetes mellitus," (in eng), *Acta Pharm Sin B*, vol. 14, no. 2, pp. 437-454, Feb 2024, doi: 10.1016/j.apsb.2023.09.004.
- [4] X. Yang, S. Yao, J. An, H. Jin, H. Wang, and B. Tuo, "SLC26A6 and NADC-1: Future direction of nephrolithiasis and calculus-related hypertension research (Review)," *Mol Med Rep*, vol. 24, no. 5, p. 745, 2021/11/01 2021, doi: 10.3892/mmr.2021.12385.
- [5] J. Wang, W. Wang, H. Wang, and B. Tuo, "Physiological and Pathological Functions of SLC26A6," (in English), *Frontiers in Medicine*, Review vol. 7, 2021-January-21 2021, doi: 10.3389/fmed.2020.618256.
- [6] H. Y. Gee *et al.*, "Mutations in SLC26A1 Cause Nephrolithiasis," *The American Journal of Human Genetics*, vol. 98, no. 6, pp. 1228-1234, 2016/06/02/ 2016, doi: 10.1016/j.ajhg.2016.03.026.
- [7] G. Hawkins-van der Ginkel, S. B. Walsh, K.-U. Eckardt, and F. Knauf, "Oxalate Metabolism: From Kidney Stones to Cardiovascular Disease," *Mayo Clinic Proceedings*, vol. 99, no. 7, pp. 1149-1161, 2024, doi: 10.1016/j.mayocp.2024.02.006.
- [8] N. Cornière *et al.*, "Dominant negative mutation in oxalate transporter SLC26A6 associated with enteric hyperoxaluria and nephrolithiasis," *Journal of Medical Genetics*, vol. 59, no. 11, p. 1035, 2022, doi: 10.1136/jmedgenet-2021-108256.
- [9] I. Sabolić, A. R. Asif, W. E. Budach, C. Wanke, A. Bahn, and G. Burckhardt, "Gender differences in kidney function," *Pflügers Archiv - European Journal of Physiology*, vol. 455, no. 3, pp. 397-429, 2007/12/01 2007, doi: 10.1007/s00424-007-0308-1.
- [10] S. Cabała, M. Ożgo, and A. Herosimczyk, "The Kidney–Gut Axis as a Novel Target for Nutritional Intervention to Counteract Chronic Kidney Disease Progression," *Metabolites*, vol. 14, no. 1, doi: 10.3390/metabo14010078.
- [11] J. Łapczuk-Romańska, M. Drożdżik, S. Oswald, and M. Drożdżik, "Kidney Drug Transporters in Pharmacotherapy," *International Journal of Molecular Sciences*, vol. 24, no. 3, doi: 10.3390/ijms24032856.
- [12] C. Gao, X. Fu, Q. Chu, J. Li, and G. Shu, "Relationship between the ApoE gene polymorphism and type 2 diabetes mellitus complications," *Genetic Testing and Molecular Biomarkers*, vol. 25, no. 2, pp. 111-115, 2021.
- [13] S. N. Bhupathiraju and F. B. Hu, "Epidemiology of obesity and diabetes and their cardiovascular complications," *Circulation research*, vol. 118, no. 11, pp. 1723-1735, 2016.
- [14] U. Zafar, S. Khaliq, and K. P. Lone, "Genetic association of apolipoprotein A5-1131T> C polymorphism with traits of metabolic syndrome," *J Coll Physicians Surg Pak*, vol. 29, no. 7, pp. 626-30, 2019.
- [15] S. Vadakedath and V. Kandi, "Probable Potential Role of Urate Transporter Genes in the Development of Metabolic Disorders," *Cureus*, vol. 10, no. 3, p. e2382, 2018/3/28 2018, doi: 10.7759/cureus.2382.
- [16] A. Pfau *et al.*, "SLC26A1 is a major determinant of sulfate homeostasis in humans," *The Journal of clinical investigation*, vol. 133, no. 3, p. e161849, doi: 10.1172/jci161849.
- [17] V. Tasic *et al.*, "Clinical and Functional Characterization of URAT1 Variants," *PLOS ONE*, vol. 6, no. 12, p. e28641, 2011, doi: 10.1371/journal.pone.0028641.
- [18] Y. Ma, H. Lv, J. Wang, and J. Tan, "Heterozygous mutation of SLC34A1 in patients with hypophosphatemic kidney stones and osteoporosis: a case report," *Journal of International Medical Research*, vol. 48, no. 3, p. 0300060519896146, 2020, doi: 10.1177/0300060519896146.
- [19] O. Polasek *et al.*, "Association of nephrolithiasis and gene for glucose transporter type 9 (SLC2A9): study of 145 patients," (in eng), *Croat Med J*, vol. 51, no. 1, pp. 48-53, Feb 2010, doi: 10.3325/cmj.2010.51.48.
- [20] J. Le *et al.*, "Restoration of mRNA expression of solute carrier proteins in liver of diet-induced obese mice by metformin," *Frontiers in endocrinology*, vol. 12, p. 720784, 2021.
- [21] D.-y. Chen *et al.*, "Comprehensive analyses of solute carrier family members identify SLC12A2 as a novel therapy target for colorectal cancer," *Scientific Reports*, vol. 14, no. 1, p. 4459, 2024/02/23 2024, doi: 10.1038/s41598-024-55048-y.
- [22] J. Du *et al.*, "The impact of solute carrier proteins on disrupting substance regulation in metabolic disorders: insights and clinical applications," (in English), *Frontiers in Pharmacology*, Review vol. Volume 15 - 2024, 2025-January-09 2025, doi: 10.3389/fphar.2024.1510080.



This is an open-access article distributed under the terms of the Creative Commons Attribution License.