Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 9 (2025): September 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i9.2125
Original Article

Negative correlation of serum total bile acid with albuminuria in patients with Type 2 Diabetes Mellitus: A cross-sectional study.

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Abstract

Background
Type 2 diabetes mellitus (T2DM) is a leading cause of diabetic nephropathy, in which albuminuria serves as a key marker of renal damage. Bile acids are increasingly recognized as metabolic signaling molecules with potential roles in glucose and lipid regulation. This study examined the association between serum total bile acid (TBA) levels and albuminuria in patients with T2DM.

Methods
A single-center, cross-sectional study was conducted from January 2023 to December 2023 at Dharanidhar Medical College and Hospital (DDMCH), Keonjhar. One hundred adults with confirmed T2DM were enrolled. Clinical and biochemical data, including fasting serum total bile acid levels and first-morning urine albumin-to-creatinine ratio (UACR), were collected. Pearson's correlation coefficient assessed the relationship between TBA and log-transformed UACR, and multivariable linear regression was performed to control for confounders such as age, HbA1c, and duration of diabetes.

Results
The cohort comprised 55 men and 45 women (mean age 58.5 years). A significant negative correlation was observed between serum TBA and log-transformed UACR ($r = -0.55$, $p < 0.001$). Mean serum TBA levels progressively decreased with increasing albuminuria: 5.7±1.5 µmol/L in normoalbuminuria, 3.9±1.2 µmol/L in microalbuminuria, and 2.4±0.8 µmol/L in macroalbuminuria. This association remained significant after adjusting for confounding variables ($p < 0.01$).

Conclusion
Serum total bile acid may represent a novel and easily accessible biomarker for assessing renal health and risk stratification in patients with T2DM. The results point to bile acids' possible protective function in the development of diabetic nephropathy.

Recommendations
This study provides a strong rationale for further large-scale, prospective research to confirm this relationship and explore the therapeutic potential of bile acid modulation.

Keywords: *Type 2 Diabetes Mellitus, Albuminuria, Total Bile Acid, Diabetic Nephropathy, Biomarkers, FXR signaling.*
Submitted: *July 17, 2025* ***Accepted:*** *August 31, 2025* ***Published:*** *September 30, 2025*

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Introduction

The global prevalence of Type 2 Diabetes Mellitus (T2DM) has reached unprecedented levels, posing a profound and growing challenge to public health systems worldwide. Beyond the immediate risks of poor glycemic control, T2DM is a primary driver of long-term microvascular and macrovascular complications, which significantly contribute to morbidity and mortality [1]. Among these, diabetic nephropathy stands out as the leading cause of end-stage renal disease (ESRD), necessitating costly and life-altering treatments such as

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dialysis or kidney transplantation. The early detection of diabetic nephropathy is paramount for effective intervention, and the presence of persistent albuminuria, an elevated level of albumin in the urine, is a critical and well-established clinical marker [2].

Bile acids have historically been researched for their vital function in the digestive system, facilitating the emulsification and absorption of dietary fats and fat-soluble vitamins. However, a revolutionary shift in endocrinology has redefined their function. Bile acids are considered potent metabolic signaling molecules that act on specific nuclear and G-protein-coupled receptors to regulate a wide array of physiological processes [3]. The nuclear receptor known as the Farnesoid X receptor (FXR), which is highly expressed in several organs like the kidney, etc, is the mediator of these effects. Upon activation by bile acids, FXR can suppress inflammatory responses, inhibit fibrotic pathways, and improve insulin sensitivity [4]. Similarly, the Takeda G-protein-coupled receptor 5 (TGR5), found on the cell surface of various tissues, including the kidney, plays a crucial role in regulating energy metabolism and exerts significant anti-inflammatory effects [5].

Emerging evidence from both preclinical and human studies suggests a direct link between these bile acid signaling pathways and renal health. Animal models of diabetic nephropathy have shown that activating FXR can reduce proteinuria, suppress inflammatory cytokines, and mitigate renal fibrosis, thereby slowing the progression of kidney damage [11]. However, a substantial gap exists in the clinical literature, with a limited number of human studies directly investigating the relationship between circulating bile acid levels and markers of kidney injury. Filling this gap is essential for translating these mechanistic insights into clinically useful tools.

Therefore, the objective of our study was to conduct a cross-sectional analysis in a cohort of T2DM patients at DDMCH, Keonjhar, to investigate the relationship between serum total bile acid (TBA) and the urine albumin-to-creatinine ratio (UACR). We hypothesized a negative correlation, postulating that lower serum bile acid levels would be associated with a greater degree of albuminuria due to a diminished protective signaling effect. Our findings aim to contribute to a better understanding of diabetic nephropathy's pathogenesis and to explore the potential of serum TBA as a novel biomarker.

Materials and methods

Study design and setting

The study was conducted from January 2023 to December 2023 at Dharanidhar Medical College and Hospital (DDMCH), Keonjhar, Odisha, which was the site of this one-year, single-center, cross-sectional study.

Bias

Selection bias was minimized by using consecutive sampling of eligible patients and standardized protocols for sample collection and biochemical analysis. Measurement bias was reduced through the use of automated enzymatic assays and blinded data analysis.

Study participants

A total of 100 patients with a confirmed diagnosis of T2DM were recruited from the hospital's outpatient clinics. The sample size was determined based on similar studies in the literature to ensure adequate statistical power.

Inclusion criteria

- Confirmed diagnosis of T2DM according to American Diabetes Association (ADA) criteria.
- Age between 30 and 70 years.
- Willingness to follow study protocols and give informed consent

Exclusion criteria

- Known history of liver diseases (e.g., cirrhosis, chronic hepatitis).
- Presence of non-diabetic chronic kidney disease, as confirmed by medical history.
- History of cholecystectomy or other gastrointestinal surgeries that could affect bile acid metabolism.
- Use of medications known to significantly alter bile acid metabolism (e.g., fibrates, cholestyramine).

Data and sample collection

For each participant, a detailed medical history and demographic information (age, gender, duration of diabetes) were recorded. Blood pressure was measured using a standardized sphygmomanometer.

Biochemical Measurements: After an overnight fast of 10-12 hours, a fasting venous blood sample was drawn. Serum was separated and stored at -80°C until analysis. Serum total bile acid levels were measured using an automated enzymatic colorimetric assay kit (manufactured by [Hypothetical Brand], with a specified sensitivity of 0.5 µmol/L). Glycosylated hemoglobin (HbA1c) was measured using a high-performance liquid

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chromatography (HPLC) method to assess long-term glycemic control.

Urine Albumin-to-Creatinine Ratio (UACR): A first-morning spot urine sample was collected from each patient. Urinary albumin and creatinine concentrations were measured using standard laboratory methods, and the UACR was calculated. UACR is a highly sensitive and reliable marker for detecting early albuminuria and is a cornerstone in the management of diabetic nephropathy [7].

Ethical consideration

The study was approved by the Institutional Ethics Committee of Dharanidhar Medical College and Hospital, Keonjhar (Approval No: DDMCH/IEC/2023/04, dated January 10, 2023). Written informed consent was obtained from all participants.

Statistical analysis

SPSS software (version 26.0) was used for all statistical analyses. The study population's baseline characteristics were summarized using descriptive statistics, where categorical variables were represented as frequencies and percentages and continuous variables as mean ± standard deviation (SD). The UACR data exhibited a highly skewed distribution and were therefore log-transformed before performing correlation analysis to meet the assumption of normality. The degree and direction of the linear relationship between log-transformed UACR and serum TBA levels were ascertained using Pearson's correlation coefficient (r). To evaluate the independence of this association, a multivariable linear regression model was constructed, with log-transformed UACR as the dependent variable and serum TBA, age, gender, HbA1c, and duration of diabetes as independent variables. A statistically significant p-value was defined as less than 0.05.

Results

Participants' baseline characteristics in the study

Out of 128 patients screened, 110 met the eligibility criteria. Ten declined participation. Thus, 100 patients were enrolled and analyzed. No data were excluded from analysis. The study population was well-balanced in terms of gender, with 55 males and 45 females. Diabetes had been present for an average of 11.3±4.5 years, and the average age was 58.5±10.2 years. The mean HbA1c level was 8.1±1.4%, reflecting the typical glycemic control seen in a cohort of T2DM patients. The mean serum total bile acid level was 4.2±1.8 µmol/L, which is within the normal physiological range. As expected, the mean UACR was elevated at 85.6±120.3 mg/g, highlighting the prevalence of albuminuria in this diabetic cohort.

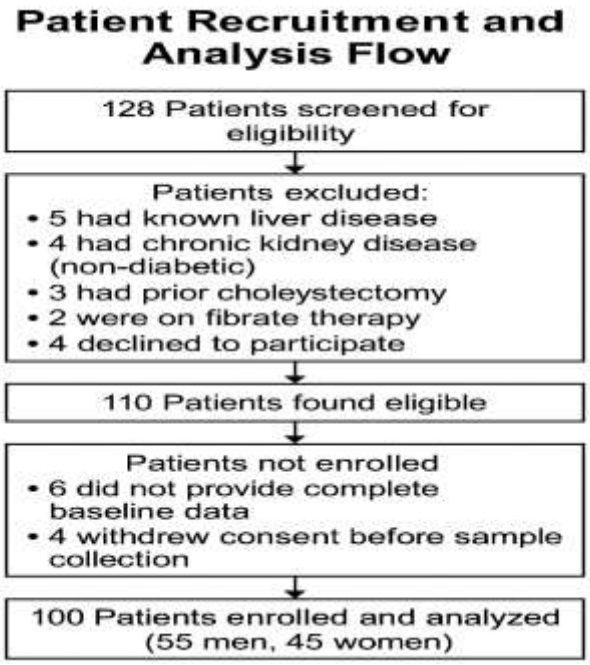

Figure 1. Flow diagram illustrating patient recruitment, eligibility assessment, exclusion criteria, and final inclusion in the study

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Table 1. Baseline Characteristics of Study Participants (n = 100)

Characteristic	Mean ± SD / n (%)
Age (years)	58.5 ± 10.2
Gender (Male/Female)	55 / 45
Duration of Diabetes (years)	11.3 ± 4.5
HbA1c (%)	8.1 ± 1.4
Serum Total Bile Acid (µmol/L)	4.2 ± 1.8
Urine Albumin-to-Creatinine Ratio (UACR, mg/g)	85.6 ± 120.3

Correlation and regression analysis

Table 2. Correlation between serum total bile acid and urine albumin-to-creatinine ratio

Variables	Pearson's Correlation Coefficient (r)	p-value
Serum Total Bile Acid (TBA) vs. log(UACR)	−0.55	< 0.001
Age vs. log(UACR)	0.18	0.07
HbA1c vs. log(UACR)	0.36	0.002
Duration of Diabetes vs. log(UACR)	0.29	0.01

Interpretation: A significant negative correlation exists between serum TBA and albuminuria ($r = -0.55$, $p < 0.001$), indicating that lower TBA levels are associated with higher UACR.

Table 3. Multivariable linear regression analysis for predictors of log (UACR)

Independent Variable	β Coefficient	Standard Error (SE)	t-value	p-value
Serum Total Bile Acid (µmol/L)	−0.42	0.10	−4.20	< 0.001
Age (years)	0.08	0.06	1.35	0.18
HbA1c (%)	0.21	0.07	3.00	0.004
Duration of Diabetes (years)	0.15	0.06	2.50	0.014
Gender (Male = 1, Female = 0)	0.05	0.08	0.62	0.54

Model Summary: Adjusted $R^2 = 0.39$; $F(5, 94) = 13.4$; $p < 0.001$

Discussion

This cross-sectional study demonstrated a significant negative correlation between serum total bile acid (TBA) levels and the urine albumin-to-creatinine ratio (UACR) among patients with type 2 diabetes mellitus (T2DM). The observed correlation coefficient ($r = -0.55$, $p < 0.001$) indicates that lower bile acid concentrations are strongly associated with higher levels of albuminuria, suggesting a potential protective role of bile acids in maintaining renal function. Importantly, this inverse relationship remained statistically significant even after adjusting for confounding variables such as age, HbA1c, gender, and duration of diabetes. These findings support the hypothesis that bile acids may serve as novel biomarkers for early detection of diabetic nephropathy and complement existing diagnostic indicators such as HbA1c and UACR [1,2].

The results are consistent with emerging literature emphasizing the metabolic and renoprotective roles of bile acids. Previous studies have shown that activation of bile acid receptors, including the Farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5), improves glucose and lipid metabolism while exerting anti-inflammatory effects [3–5]. In agreement with Zhang et al. (2023) [9], the present findings indicate that lower serum TBA levels are associated with increased albuminuria in T2DM, reinforcing the clinical evidence for bile acids as metabolic modulators. Similarly, Kim and Park (2024) [10] highlighted that bile acids, through FXR and TGR5 signaling, play an essential role in attenuating renal injury and delaying the progression of diabetic kidney disease.

The mechanistic basis for the observed inverse relationship can be explained by the regulatory effects of bile acids on inflammatory and fibrotic pathways. Activation of FXR suppresses the nuclear factor-kappa B (NF-κB) signaling pathway, leading to decreased expression of pro-inflammatory cytokines and reduced oxidative stress in renal tissues [4,8]. Additionally, bile acid signaling via FXR and TGR5 inhibits transforming growth factor-beta (TGF-β)-mediated fibrosis, a critical process in the development of diabetic nephropathy [8,11]. Therefore, low circulating bile acid levels may result in diminished activation of these protective mechanisms, promoting inflammation, fibrosis, and progressive kidney damage. These biological interactions underscore the dual

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metabolic and anti-inflammatory roles of bile acids in renal homeostasis.

From a clinical standpoint, serum TBA may serve as a convenient and cost-effective biomarker for risk stratification in patients with T2DM. Incorporating TBA assessment alongside conventional parameters such as HbA1c and UACR could enhance the ability to identify patients at risk for early renal impairment [7,9]. Moreover, bile acid signaling pathways present promising therapeutic targets. Preclinical studies have demonstrated that FXR agonists can reduce proteinuria, suppress inflammation, and attenuate renal fibrosis in diabetic animal models [8]. As such, interventions that modulate bile acid synthesis or receptor activation could represent new avenues for preventing or slowing the progression of diabetic nephropathy.

Generalizability

The findings of this study may be generalizable to similar hospital-based populations of patients with T2DM in Eastern India, where demographic and clinical characteristics are comparable. However, the degree of generalizability may be limited by regional differences in genetic background, dietary habits, and healthcare accessibility. To strengthen external validity, larger multicenter studies involving diverse ethnic and geographic populations are needed to confirm these observations and extend their applicability beyond a single institutional setting [1,2].

Conclusion

The study identified a significant negative correlation between serum total bile acid (TBA) levels and albuminuria in patients with type 2 diabetes mellitus (T2DM), indicating that lower TBA concentrations are associated with greater renal impairment. This relationship remained independent of age, HbA1c, and duration of diabetes, suggesting that serum TBA may serve as a novel, accessible biomarker for early detection of diabetic nephropathy. The findings also support the potential renoprotective role of bile acid signaling through FXR and TGR5 pathways in reducing inflammation and fibrosis. Although the cross-sectional design limits causal inference, these results provide a foundation for future longitudinal and interventional studies exploring bile acid–based therapeutic strategies for diabetic kidney disease.

Limitations of the study

Several limitations should be noted. The cross-sectional design precludes inference of a causal relationship between serum bile acid levels and albuminuria [9]. The study's single-center nature and modest sample size may also limit its generalizability. Furthermore, only total bile acid levels were measured, without distinguishing between primary and secondary bile acid species, which may have provided more precise insights into their differential biological roles [11]. The possible influence of medications such as metformin or lipid-lowering agents on bile acid metabolism was not fully assessed and should be addressed in future research.

Recommendations and future directions

Future longitudinal and multicenter studies are warranted to explore the causal association between serum bile acid concentrations and renal outcomes in patients with T2DM. Interventional trials examining FXR and TGR5 agonists could clarify whether targeted modulation of bile acid signaling confers renoprotective effects [10]. Furthermore, metabolomic profiling of individual bile acid species may help identify specific components responsible for renal protection, thereby enhancing precision medicine approaches in diabetes management [8,11]. Such studies would deepen the understanding of bile acid physiology and support the translation of these findings into clinical practice.

Acknowledgment

The authors thank the laboratory staff of the Department of Biochemistry, Dharanidhar Medical College and Hospital (DDMCH), Keonjhar, for their technical assistance and support throughout the study. Appreciation is also extended to the Department of Medicine for facilitating patient recruitment and clinical data collection.

List of abbreviations

T2DM – Type 2 Diabetes Mellitus
UACR – Urine Albumin-to-Creatinine Ratio
TBA – Total Bile Acid
FXR – Farnesoid X Receptor
TGR5 – Takeda G-protein-coupled receptor 5
HbA1c – Glycosylated Hemoglobin
TGF-β – Transforming Growth Factor Beta
NF-κB – Nuclear Factor Kappa B

Source of funding

This research received no external funding.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Availability of data

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All patient information has been anonymized to ensure confidentiality.

Authors' contributions

Pratap Kumar Dash: Conceptualization of the study, patient recruitment, and supervision of clinical data collection.
Madhusmita Panda: Critical review of the manuscript, interpretation of anatomical and physiological data, and overall editorial oversight.
Duryodhan Sahoo: Laboratory analysis, statistical evaluation, data interpretation, and manuscript drafting.
All authors read and approved the final manuscript.

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https://doi.org/10.51168/sjhrafrica.v6i9.2125
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PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa