RESEARCH PAPER

Serum Irisin as a Potential Biomarker of Diabetic Nephropathy Severity in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic nephropathy (DN) is a major microvascular complication of type 2 diabetes mellitus (T2DM). Irisin, a myokine involved in metabolic regulation, has been reported to decrease with deteriorating renal function Therefore, serum irisin may serve as a potential biomarker for assessing the severity of DN in patients with T2DM.

Objectives: To evaluate serum irisin as a biomarker of diabetic nephropathy severity in patients with type 2 diabetes mellitus and to assess their relationship with renal and metabolic parameters.

Methodology: A case-control study was conducted at Aswan University Hospital, including 93 participants: 31 controls and 62 patients with Type 2 Diabetes, who were further subdivided according to albuminuria into 31 normoalbuminuric diabetic patients, 10 micro-albuminuric DN patients and 21 macro-albuminuric DN patients. Demographic data, blood pressure, glycemic indices, lipid profile, renal function parameters, and serum irisin levels were assessed.

Results: Mean circulating irisin levels showed a significant and progressive reduction with increasing albuminuria severity, decreasing from 305.34 ± 119.89 ng/mL in controls to 189.79 ± 44.08 ng/mL in normoalbuminuria, 123.83 ± 9.49 ng/mL in microalbuminuria, and 63.10 ± 23.59 ng/mL in macroalbuminuria DN patients.

Conclusion: Circulating irisin levels progressively decline with worsening diabetic nephropathy and increasing albuminuria in type 2 diabetes patients.

Keywords: Irisin, Type 2 diabetes mellitus, Diabetic nephropathy
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INTRODUCTION

Type 2 diabetes (T2D) accounts for nearly 98% of all diabetes cases worldwide, and its global prevalence is increasing rapidly. ***(Green et al., 2021).*** **(1)**

In individuals with diabetes, chronic kidney disease (CKD) typically develops after about 10 years in Type 1 diabetes (T1D) most commonly 5–15 years after diagnosis but may already be present at the time of T2D diagnosis. ***(Johansen et al., 2021).*** **(2)**

Not all individuals with diabetes develop diabetic nephropathy (DN). Major risk factors include poor glycemic control, uncontrolled hypertension, T1D with onset before 20 years of age, current or past smoking, and a family history of DN. Genetic susceptibility also contributes ***(Zhu et al., 2025).*** **(3)**

Currently, DN is the leading cause of CKD. Diabetes accounts for approximately 30–40% of all End stage renal disease (ESRD) cases in the United States. ***(Habas et al., 2025).*** **(4)**

DN progresses through several clinical stages, beginning with glomerular hyperfiltration, followed by microalbuminuria, macroalbuminuria, nephrotic-range proteinuria, and ultimately progressive CKD leading to ESRD. ***(Lin et al., 2018).*** **(5)**

Albuminuria was categorized into normo-albuminuria (<30 mg/g creatinine), micro-albuminuria (30–300 mg/g creatinine), and macro-albuminuria (>300 mg/g creatinine). ***(Rasaratnam et al., 2024).*** **(6)**

CKD in people with diabetes is usually diagnosed clinically based on albuminuria and/or reduced estimated glomerular filtration

rate (eGFR), in the absence of other primary kidney diseases. Typical features include long-standing diabetes, diabetic retinopathy, albuminuria without gross hematuria, and a gradual decline in eGFR ***(Vistisen et al., 2019).*** **(7)**

Irisin is generated from its precursor, fibronectin type III domain-containing protein 5 (FNDC5), through proteolytic cleavage of its extracellular domain, after which it is released into the peripheral circulation. ***(Grzeszczuk et al., 2024).*** **(8)**

Serum irisin levels show a marked decline as CKD progresses, with the lowest concentrations observed in individuals with stage 5 CKD. (***Aboutorabi et al., 2025).*** **(9)**

Although albuminuria and eGFR currently serve as the primary diagnostic and prognostic markers for DN, both parameters have some limitations. Consequently, there is an increasing need for novel biomarkers that can enhance risk assessment and enable earlier detection of the disease. (***Pillai, A., & Fulmali, D. 2023).*** **(10)**

So, we aim to evaluate serum irisin as a biomarker of diabetic nephropathy severity in patients with type 2 diabetes mellitus.

PATIENTS AND METHODS

A case-control study was conducted at Aswan University Hospital, including 93 participants: 31 controls and 62 patients with T2D, who were further subdivided according to albuminuria into 31 normoalbuminuric diabetic patients, 10 micro-albuminuric DN patients and 21 macro-albuminuric DN patients.

Inclusion criteria: Individuals with T2D aged between 40 and 70 years.

Exclusion criteria: Type 1 diabetes, pregnancy, acute infection, and impaired liver function.

Sample size: The required sample size was performed using the G*Power statistical package program Version 3.1.9.7 **(Franz Faul, Universitat Kiel, Germany)** using two population means formula for this study design. using F test (ANOVA, fixed effect, one way) and the following assumptions: Confidence level=99%; Power (1-β): 80%; Effect size=0.4 (large); Two tail.

Methods:

All participants underwent detailed history taking, including diabetes duration and medication history, followed by a full clinical examination with vital sign assessment, anthropometric measurements, BMI calculation, and chest, cardiac, fundus, and neurological evaluations.

Laboratory investigations: Fasting blood glucose (FBG), postprandial blood glucose (PP), glycosylated haemoglobin (HbA1c), renal function test (serum creatinine, urea) and lipid profile (Serum triglycerides, Total cholesterol), Albumin to creatinine ratio (ACR), urinary albumin (mg), and creatinine (g), eGFR was calculated by the CKD-EPI equations, serum irisin was measured by enzyme-linked immunosorbent assay (ELISA) kits. (SinoGeneClon Biotech -Cat. No: 11594) and diabetic patients were identified based on the American Diabetes Association diagnostic criteria, which include elevated A1C levels (≥ 6.5%), increased FBG (≥ 126 mg/dL), abnormal 2-hour PP glucose values (≥ 200 mg/dL) during a 75-g OGTT, or a random plasma glucose concentration ≥ 200 mg/dL accompanied by classic symptoms of hyperglycemia.

Ethical considerations:

The research protocol was approved by the relevant Scientific and Ethical Committees at the Faculty of Medicine, Aswan University. Informed written consent was secured from all participants, who were advised of their right to discontinue participation at any stage without affecting their medical care.

Statistical analysis

The collected data were coded, tabulated, and analyzed using SPSS (Statistical Package for the Social Sciences), version 29 (IBM Corp., Armonk, NY, USA) on an IBM-compatible computer. Descriptive statistics included frequencies and percentages for qualitative variables and mean ± standard deviation for quantitative measures.

The statistical tests used in this study included Chi-square test (χ^2), Student's t-test, Mann–Whitney U test, one-way ANOVA (F-test), Kruskal–Wallis test, and Pearson's correlation coefficient. Differences were considered significant when $p < 0.05$ and highly significant when $p < 0.001$.

RESULTS

This was a case-control study, conducted at Aswan University Hospital. Overall, 93 individuals participated in the present study.

Mean age was comparable across controls (56.87 ± 8.16 years), normoalbuminuric diabetics (58.45 ± 7.55 years), microalbuminuric diabetics (62.10 ± 8.45 years), and macroalbuminuric diabetics (60.38 ± 6.23 years), with no statistically significant difference among groups ($p > 0.05$).Mean BMI values were comparable across groups, measuring 26.84 ± 5.44 kg/m² in controls, 28.19 ± 4.22 kg/m² in normoalbuminuric diabetics, 28.47 ± 3.34 kg/m² in microalbuminuric diabetics, and 29.30±4.22

kg/m² in macroalbuminuric diabetics, with no statistically significant difference ($p > 0.05$).(**Table 1 and Figure 1)**

Mean duration of diabetes increased progressively with albuminuria severity, from normoalbuminuria (7.16 ± 2.27 years) to microalbuminuria (11.20 ± 3.33 years) and macroalbuminuria (14.48 ± 3.11 years), showing a statistically significant difference among diabetic subgroups ($p < 0.001$). (**Table 1 and Figure 2)**

Mean SBP showed a significant stepwise increase from controls (116.77 ± 8.32 mmHg) to normoalbuminuria (128.71 ± 7.18 mmHg), microalbuminuria (143.50 ± 10.01 mmHg), and macroalbuminuria groups (164.29 ± 7.46 mmHg) ($p< 0.001$). Mean DBP increased significantly with worsening albuminuria, from 76.77 ± 8.32 mmHg in controls to 83.87 ± 6.15 mmHg in normoalbuminuria, 90.00 ± 6.24 mmHg in microalbuminuria, and 108.10 ± 8.73 mmHg in macroalbuminuria DN patients ($p < 0.001$). (**Table 1 and Figure 3)**

Table (1): Comparison of demographic and biochemical parameters of controls and diabetic patients according to albuminuria

	Controls N=31	Normoalbuminuria N=31	Microalbuminuria N=10	Macroalbuminuria N=21	P-value
Age (Year)					
Mean±SD	56.87 ± 8.16	58.45 ± 7.55	62.10 ± 8.45	60.38 ± 6.23	0.190
Min.-Max.	45 - 70	45 - 70	46 - 70	47 - 69	
BMI					
Mean±SD	26.84 ± 5.44	28.19 ± 4.22	28.47 ± 3.34	29.30 ± 4.22	0.291
Min.-Max.	19.-20 - 37.18	18.81 - 37.95	23.55 - 34.29	21.71 - 35.46	
Duration (Year)					
Mean±SD		7.16 ± 2.27	11.20b ± 3.33	14.48b,c ± 3.11	<0.001**
Min.-Max.		4 - 14	7 - 16	10 - 18	
SBP					
Mean±SD	116.77 ± 8.32	128.71a ± 7.18	143.50a,b ± 10.01	164.29 a.b.c ± 7.46	<0.001**
Min.-Max.	100 - 130	120 - 140	120 - 150	160 - 180	
DBP					
Mean±SD	76.77 ± 8.32	83.87a ± 6.15	90.00 a,b ± 6.24	108.10 a.b.c ± 8.73	<0.001**

BMI: body mass index; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure **a** < 0.05 vs. controls; **b** < 0.05 vs. diabetics with normoalbuminuria; **c** < 0.05 vs. diabetics with microalbuminuria

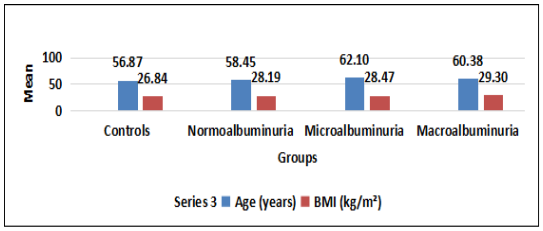

Figure (1): Comparison between controls and diabetic patients according to albuminuria as regards age and BMI

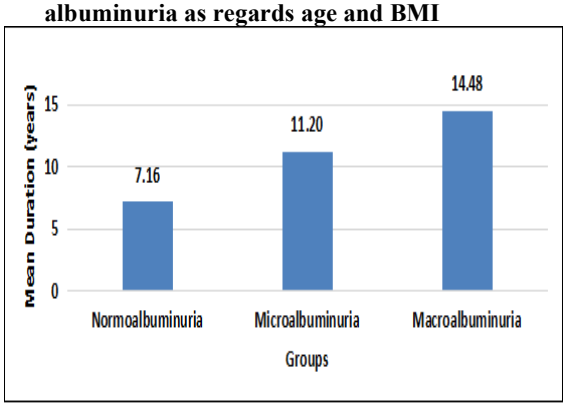

Figure (2): Comparison between controls and diabetic patients according to albuminuria as regards duration of diabetes

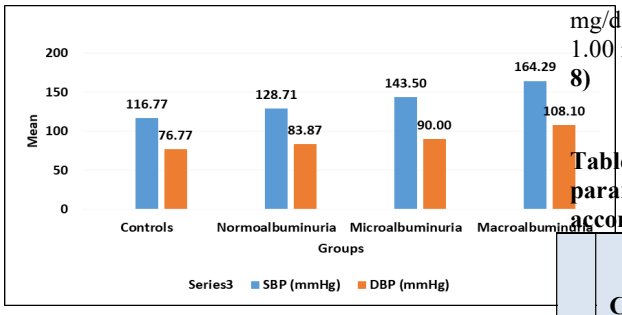

Figure (3): Comparison between controls and diabetic patients according to albuminuria as regards SBP and DBP

Mean HbA1c levels differed significantly among groups, rising from controls (4.85 ± 0.57%) to normoalbuminuric diabetics (6.45 ± 0.44%), microalbuminuric diabetics (8.32 ± 0.54%), and macroalbuminuric diabetics (10.77 ± 1.49%) ($p < 0.001$). (**Table 2 and Figure 4)**

Mean FPG increased significantly across groups, being 92.84 ± 11.28 mg/dL in controls, 146.61 ± 13.99 mg/dL in normoalbuminuria, 163.40 ± 19.37 mg/dL in microalbuminuria, and 187.95 ± 15.52 mg/dL in macroalbuminuria ($p < 0.001$). Mean PPBG demonstrated a marked and significant rise with albuminuria severity, increasing from 110.35 ± 11.18 mg/dL in controls to 212.55 ± 17.19 mg/dL in normoalbuminuria, 276.60 ± 45.11 mg/dL in microalbuminuria, and 320. 48 ± 41.28 mg/dL in macroalbuminuria DN patients ($p < 0.001$). (**Table 2 and Figure 5)**

Mean TC levels increased significantly from controls (159.71 ± 24.79 mg/dL) to normoalbuminuria (219.87 ± 64.37 mg/dL), microalbuminuria (221.10 ± 60.53 mg/dL), and macroalbuminuria groups (270.52 ± 59.45 mg/dL) ($p < 0.001$).Mean TG levels were significantly higher with advancing albuminuria, rising from 108.06 ± 17.78 mg/dL in controls to 149.35 ± 39.15 mg/dL in normoalbuminuria, 186.00 ± 47.42 mg/dL in microalbuminuria, and 219.33 ± 45.01 mg/dL in macroalbuminuria ($p < 0.001$). (**Table 2 and Figure 6)**

Mean serum urea increased significantly across groups, measuring 18.10 ± 8.59 mg/dL in controls, 29.90 ± 5.08 mg/dL in normoalbuminuria, 119.20 ± 42.75 mg/dL in microalbuminuria, and 101.29 ± 35.71 mg/dL in macroalbuminuria DN patients ($p < 0.001$). (**Table 2 and Figure 7)**

Mean serum creatinine showed a significant progressive rise from controls (0.81 ± 0.11 mg/dL) to normoalbuminuria (1.10 ± 0.11 mg/dL), microalbuminuria (2.62 ± 0.52 mg/dL), and macroalbuminuria groups (4.14 ± 1.00 mg/dL) ($p < 0.001$). (**Table 2 and Figure 8)**

Table (2): Comparison of biochemical parameters of controls and diabetic patients according to albuminuria

	Controls N=31	Normoalbuminuria N=31	Microalbuminuria N=10	Macroalbuminuria N=21	P-value
HBA1C					
Mean±SD	**4.85± 0.57**	**6.45± 0.44a**	**8.32± 0.54a, b**	**10.77± 1.49a.b.c**	**<0.001***
Min.-Max.	**4.0 - 5.6**	**5.9 - 7.9**	**7.2 - 9.4**	**8.7 - 14.0**	
FPG					
Mean±SD	**92.84± 11.28**	**146.61a ± 13.99**	**163.40 ± 19.37a,b**	**187.95 ± 15.52a.b.c**	**<0.001***
Min.-Max.	**70 - 109**	**92 - 160**	**120 - 198**	**164 - 220**	
PPBG					
Mean±SD	**110.35± 11.18**	**212.55a ± 17.19**	**276.60 ± 45.11a,b**	**320.48 ± 41.28a.b.c**	**<0.001***
Min.-Max.	**91 - 130**	**159 - 240**	**200 - 342**	**210 - 396**	
TC					
Mean±SD	**159.71± 24.79**	**219.87a ± 64.37**	**221.10 ± 60.53a,b**	**270.52 ± 59.45a.b.c**	**<0.001***
Min.-Max.	**120 - 200**	**120 - 345**	**140 - 300**	**150 - 390**	
TG					
Mean±SD	**108.06 ± 17.78**	**149.35a ± 39.15**	**186.00 ± 47.42a,b**	**219.33 ± 45.01a.b.c**	**<0.001***
Min.-Max.	**80 - 130**	**90 - 220**	**100 - 270**	**169 - 310**	
S. urea					
Mean±SD	**18.10± 8.59**	**29.90± 5.08a**	**119.20 ± 42.75a,b**	**101.29 ± 35.71a.b.c**	**<0.001***

Min.-Max.	7 - 35		22 - 38		62 - 190		53 - 177					
S. Cr												
Mean±SD	0.8± 1	0.11	1.10± 1	0.1	2.62± 0 a,b	0.51	4.14± a.b.c	1.00			<0.01*	
Min.-Max.	0.7- 1	1.00	0.9 - 1	1.3	1.9 - 3	3.5	2.7 - 6	6.0				

FPG: fasting plasma glucose; **PPBG:** Postprandial Blood Glucose; **TC:** total cholesterol; **TG:** triglycerides; **S. Cr:** Serum creatinine

a < 0.05 vs. controls; **b** < 0.05 vs. diabetics with normoalbuminuria; **c** < 0.05 vs. diabetics with microalbuminuria

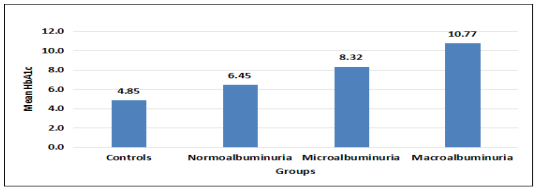

Figure (4): Comparison between controls and diabetic patients according to albuminuria as regards HbA1c level

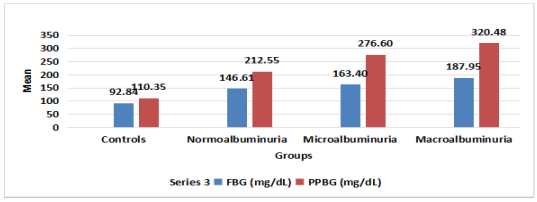

Figure (5): Comparison between controls and diabetic patients according to albuminuria as regards FPG and PPBG

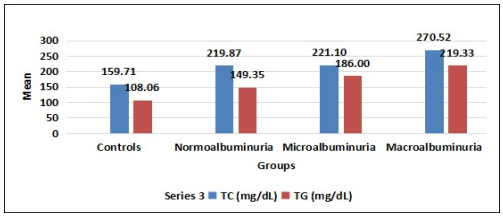

Figure (6): Comparison between controls and diabetic patients according to albuminuria as regards TC and TG levels

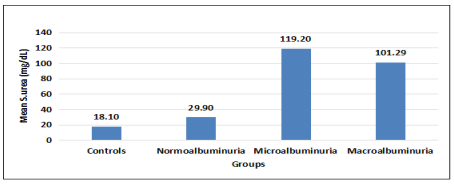

Figure (7): Comparison between controls and diabetic patients according to albuminuria as regards Serum urea

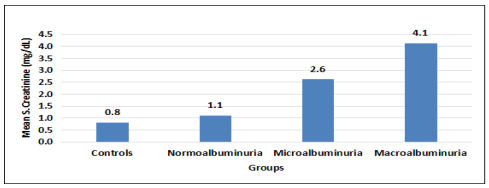

Figure (8): Comparison between controls and diabetic patients according to albuminuria as regards serum creatinine

Mean ACR increased markedly and significantly with albuminuria category, from 16.61 ± 3.77 mg/gm in controls and 20.74 ± 5.02 mg/gm in normoalbuminuria to 247.50 ± 51.49 mg/gm in microalbuminuria and 591.19 ± 189.77 mg/gm in macroalbuminuria ($p < 0.001$). (**Table 3 and Figure 9)**

Mean eGFR declined significantly across groups, from 118.12 ± 21.35 mL/min/1.73 m² in controls to 74.29 ± 10.21 mL/min/1.73 m² in normoalbuminuria, 38.16 ± 6.76 mL/min/1.73 m² in microalbuminuria, and 24.59 ± 3.88 mL/min/1.73 m² in macroalbuminuria DN patients ($p < 0.001$). (**Table 3 and Figure 10)**

Mean circulating irisin levels showed a significant and progressive reduction with increasing albuminuria severity, decreasing from 305.34 ± 119.89 ng/mL in controls to 189.79 ± 44.08 ng/mL in normoalbuminuria, 123.83 ± 9.49 ng/mL in microalbuminuria, and 63.10 ± 23.59 ng/mL in macroalbuminuria DN patients ($p < 0.001$). (**Table 3 and Figure 11)**

Table (3): Comparison of biochemical parameters of controls and diabetic patients according to albuminuria

	Controls N=31	Normoalbuminuria N=31	Microalbuminuria N=10	Macroalbuminuria N=21	P-value
ACR					
Mean±SD	16.61 ± 3.77	20.74 ± 5.02	247.50 a,b ± 51.49	591.19 a.b.c ± 189.77	<0.01*
Min.-Max.	11.- 27.	12 - 29	125 - 290	370 - 900	

.- Max.	00	00					
eGFR							
Mean±SD	118.12	± 21.35	74.29a	± 10.21	38.16 a,b	± 6.76	24.59 a.b.c	± 3.88	<0.001**
Min.- Max.	92.93	- 166.91	60.35	- 96.56	32.40	- 55.52	18.68	- 31.21	
Irisin									
Mean±SD	305.34	± 119.89	189.79a	± 44.08	123.83 a,b	± 9.49	63.10 a.b.c	± 23.59	<0.001**
Min.- Max.	203.01	- 639.26	150.37	- 272.94	110.15	- 140.22	21.18	- 97.38	

ACR: albumin creatinine ratio; **eGFR:** estimated glomerular filtration rate.
a < 0.05 vs. controls; **b** < 0.05 vs. diabetics with normoalbuminuria; **c** < 0.05 vs. diabetics with microalbuminuria

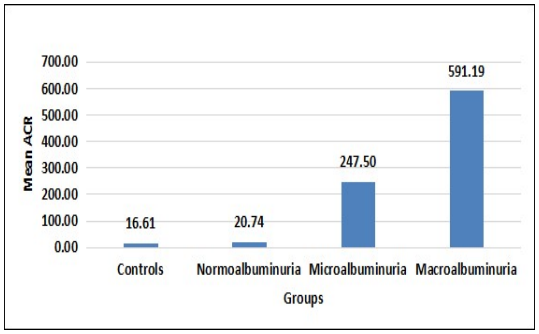

Figure (9): Comparison between controls and diabetic patients according to albuminuria as regards ACR

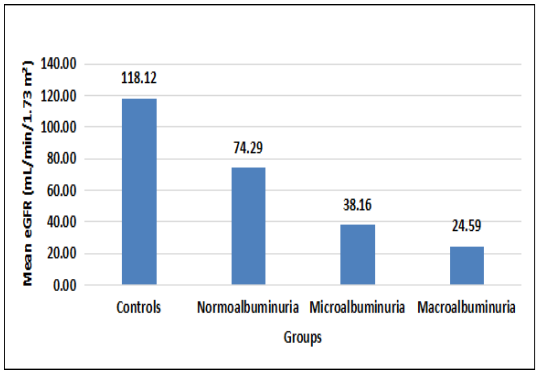

Figure (10): Comparison between controls and diabetic patients according to albuminuria as regards eGFR

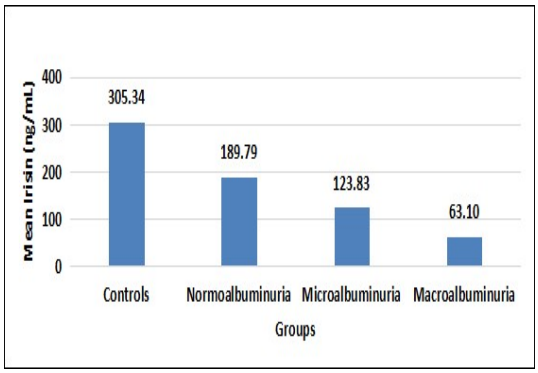

Figure (11): Comparison between controls and diabetic patients according to albuminuria as regards circulating irisin level

circulating irisin was significantly and negatively correlated with age (r = −0.409), duration of diabetes (r = −0.627), BMI (r = −0.422), SBP (r = −0.666), DBP (r = −0.575), HbA1c (r = −0.680), FBG (r = −0.694), PPBG (r = −0.595), total cholesterol (r = −0.473), TG (r = −0.604), serum urea (r = −0.596), serum creatinine (r = −0.652), and ACR (r = −0.604), with all correlations being highly statistically significant (p < 0.001).In contrast, circulating irisin showed a strong positive correlation with eGFR (r = 0.793, p < 0.001), indicating higher irisin levels in association with better renal function.**(Table 4)**

Table (4): Correlation of circulating irisin with clinical and biochemical parameters of studied groups

	Irisin	
	r	**P-value**
Age	-0.409	<0.001**
Duration	-0.627	<0.001**
BMI	-0.422	<0.001**
SBP	-0.666	<0.001**
DBP	-0.575	<0.001**
HBA1C	-0.680	<0.001**
FBG	-0.694	<0.001**
PPBG	-0.595	<0.001**
Cholesterol	-0.473	<0.001**
TG	-0.604	<0.001**
S. urea	-0.596	<0.001**
S. Creatinine	-0.652	<0.001**
ACR	-0.604	<0.001**
eGFR	0.793	<0.001**

r: Correlation coefficient, **: Highly significant P-value <0.001

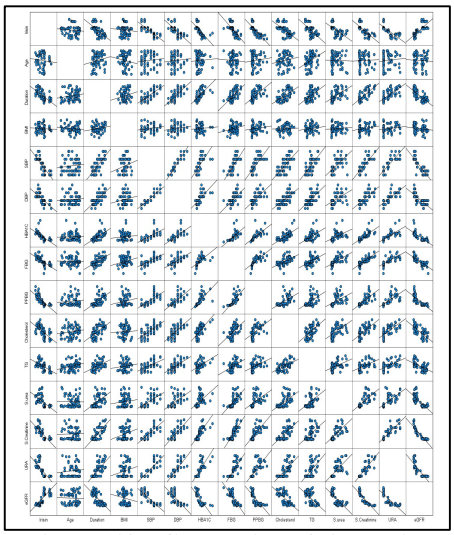

Figure (12): Correlation of circulating irisin with clinical and biochemical parameters of studied groups

DISCUSSION

The study groups had comparable ages, with no statistically significant difference among controls, normoalbuminuric, microalbuminuric, and macroalbuminuric diabetic patients ($p > 0.05$).

These findings are consistent with **Hu et al. (11)** who documented comparable ages between diabetics with nephropathy (59.1 ± 7.2 years) and those without nephropathy (57.8 ± 8.0 years), with no significant difference ($p > 0.05$).

Similarly**, Liu et al. (12)** reported similar age distributions across diabetic patients with varying degrees of renal involvement, with no significant intergroup differences.

Our study showed that patients with micro- and macroalbuminuria had a significantly longer duration of diabetes compared with normoalbuminuric patients, suggesting that prolonged exposure to hyperglycemia contributes to cumulative renal damage and increasing disease severity.

These results are consistent with **Shelbaya et al. (13)** who documented a significantly longer mean duration of diabetes in DN patients (10.93 ± 2.36 years) compared with non-nephropathic diabetics (5.0 ± 2.19 years, $p < 0.001$), also reported a strong negative correlation between serum irisin and duration of diabetes ($r = -0.942$, $p < 0.001$).

These findings also, are in agreement with **Elesawy et al. (14)** who reported highly significant longer duration of DM (8.85 and 10.3 years for those with micro- and macro-albuminuria respectively) compared to 6.6 years duration in diabetics with normo – albuminuria.

Our findings demonstrated a significant stepwise increase in mean SBP across the study groups, rising from controls (116.77 ± 8.32 mmHg) to normoalbuminuric patients (128.71 ± 7.18 mmHg), microalbuminuric patients (143.50 ± 10.01 mmHg), and reaching the highest levels in macroalbuminuric patients (164.29 ± 7.46 mmHg) ($p < 0.001$). Similarly, mean DBP increased significantly with worsening albuminuria, being lowest in controls (76.77 ± 8.32 mmHg), higher in normoalbuminuric patients (83.87 ± 6.15 mmHg), further increased in microalbuminuric patients (90.00 ± 6.24 mmHg), and highest in macroalbuminuric patients (108.10 ± 8.73 mmHg) ($p < 0.001$).

These findings are in agreement with **Shelbaya et al. (13),** who also reported that mean SBP increased significantly across groups, from controls (112.66 ± 11.12 mmHg) to diabetics (121.16 ± 7.39 mmHg) and diabetic nephropathy patients (128.66 ± 8.99 mmHg) ($p < 0.001$), also mean DBP showed a significant progressive rise, being lowest in controls, higher in diabetics, and highest in diabetic nephropathy patients ($p < 0.001$). Their results further showed a Highly statistically significant negative correlation between serum irisin and both SBP ($r = -0.493$) and DBP ($r = -0.625$), (P-value <0.001) indicating that higher blood pressure is closely linked to reduced irisin levels in T2DM patient.

Our findings indicate progressively worsening glycemic control with increasing albuminuria severity. Mean HbA1c levels differed significantly across the study groups, rising from controls to normoalbuminuric diabetics, microalbuminuric diabetics and reaching the highest levels in macroalbuminuric diabetics ($p < 0.001$).

Both mean fasting plasma glucose (FPG) and mean postprandial blood glucose (PPBG) showed a significant stepwise increase, being lowest in controls, higher in normoalbuminuric patients, further increased in microalbuminuric patients, and highest in macroalbuminuric patients ($p < 0.001$).

Circulating irisin was significantly and negatively correlated with HbA1c ($r = -0.680$), fasting blood glucose ($r = -0.694$), postprandial blood glucose ($r = -0.595$), ($p < 0.001$).

These findings are in agreement with **El Haddad et al. (15),** who reported significant negative correlations between irisin and major

glycemic markers, including fasting blood glucose (r = −0.419) (P-value=0.001), HbA1c (r = −0.528) (P-value<0.001), and urinary albumin excretion, (r = −0.439) (P-value=0.001) indicating that poorer glycemic control is associated with lower irisin levels.

Shelbaya et al. (13) also, reported higher mean HbA1c levels in DN patients (8.33 ± 1.3%) compared with diabetics without nephropathy (7.80 ± 0.8%), with no statistical significant difference as regard HbA1c (p=0.063) and FBS (p= 0.689) between groups, but also reported significant statistical negative correlation was found between irisin and HbA1c (r = −0.365) (P-value=0.048) and between irisin and FBS. (r = −0.495) (P-value= 0.005) in diabetic nephropathy patients.

In the present study, total cholesterol (TC) and triglyceride (TG) levels exhibited a clear and statistically significant progressive increase with worsening albuminuria severity. Mean TC levels rose significantly from controls to normoalbuminuric, microalbuminuric, and macroalbuminuric patients ($p < 0.001$). Likewise, mean TG levels increased markedly across the same groups, with the highest values observed in patients with macroalbuminuria ($p < 0.001$).

In our study, circulating irisin also demonstrated significant negative correlations with total cholesterol (r = −0.473) and triglycerides (r = −0.604) ($p < 0.001$). These findings reflect the well-established pattern of progressive dyslipidemia accompanying worsening glycemic control and renal involvement in type 2 diabetes associated with declining irisin levels.

Our results are in agreement with **Elesawy et al. (14),** who reported a similar progressive rise in lipid parameters across different stages of albuminuria. In their cohort, Mean TC increased from 148.72 ± 14.46 mg/dL in controls to 227.24 ± 10.23 mg/dL in normo-albuminuric diabetics, 265.95 ± 11.13 mg/dL in micro-albuminuric patients, and reached 288.30 ± 57.76 mg/dL in those with macro-albuminuria. Mean TG levels followed the same pattern, rising from 120.52 ± 11.19 mg/dL in controls to 206.30 ± 18.85 mg/dL, 277.22 ± 9.45 mg/dL, and 286.69 ± 21.93 mg/dL in normo-, micro-, and macro-albuminuric diabetic subjects respectively.

The present study demonstrated a marked deterioration in renal function with increasing albuminuria severity, mean serum urea levels and mean serum creatinine exhibited a significant progressive rise from controls to normoalbuminuric patients, microalbuminuric patients, and reached the highest levels in macroalbuminuric patients. ($p < 0.001$), reflecting a progressive decline in renal function associated with diabetes severity and duration.

In our study, circulating irisin also demonstrated significant negative correlations with serum urea (r = −0.596), serum creatinine (r = −0.652). ($p < 0.001$).

These results are consistent with **Hu et al. (11)** who found that diabetic patients with more advanced microvascular complications including nephropathy had significantly higher creatinine and blood urea nitrogen levels, accompanied by markedly lower irisin concentrations. Their results showed an inverse relationship between irisin and renal impairment markers, supporting the concept that renal dysfunction contributes to irisin decline.

In agreement with these findings, **Liu et al. (12)** demonstrated that circulating irisin levels were significantly reduced in diabetic patients with renal insufficiency compared to those with preserved renal function. The reduction in irisin was most pronounced in patients with severe impairment, highlighting a clear relationship between renal decline and irisin reduction.

In this study, mean ACR showed a marked and statistically significant increase across albuminuria categories, being lowest in controls, slightly higher in normoalbuminuric patients, and markedly elevated in microalbuminuric and macroalbuminuric patients ($p < 0.001$). circulating irisin also demonstrated significant negative correlations with ACR (r = −0.604), ($p < 0.001$).

Our results are in agreement with **Khairallah et al. (2025) (16)** who showed that mean ACR values were markedly increased in diabetics compared with controls (430.12 ± 1179.31 vs. 13.64 ± 7.36 mg/g), confirming the same pattern seen in our study.

In our study, the significant decline in eGFR with worsening albuminuria, together with its positive association with circulating irisin, highlights the close relationship between irisin levels and renal function deterioration in diabetic nephropathy.

This pattern is consistent with **Liu et al. (12)** who demonstrated that patients with reduced renal function (eGFR < 60 mL/min/1.73 m²) had significantly lower serum irisin concentrations compared with those with preserved renal function, with the decline being most evident in advanced renal insufficiency (stage 5 CKD patients).

Further supporting these findings, the systematic review and meta-analysis by **Deng et al. (17)** reported that T2D patients with

eGFR ≤ 60 mL/min/1.73 m² had lower irisin levels than those with preserved renal function, although this difference was not statistically significant.

In the present study, mean circulating irisin levels showed a significant and progressive reduction with increasing albuminuria severity. Irisin levels were highest in controls (305.34 ± 119.89 ng/mL), significantly decreased in normoalbuminuric patients (189.79 ± 44.08 ng/mL), further reduced in microalbuminuric patients (123.83 ± 9.49 ng/mL), and reached the lowest levels in macroalbuminuric patients (63.10 ± 23.59 ng/mL) ($p < 0.001$).

These findings indicate a clear inverse relationship between albuminuria severity and circulating irisin, consistent with worsening renal function and metabolic dysregulation.

Khidr et al. (18) reported that patients with T2D had significantly lower serum irisin levels compared with healthy controls. Furthermore, their findings showed a progressive decline in irisin concentrations with increasing albuminuria severity, where microalbuminuric patients demonstrated lower irisin levels than both normoalbuminuric diabetics and control subjects, with an even further reduction observed in the macroalbuminuric group.

Also, **Zhang et al. (19)** reported that serum irisin concentrations were significantly lower in newly diagnosed patients with T2D compared with healthy controls, highlighting the early decline in irisin associated with metabolic dysfunction in T2D patients.

The progressive decline in circulating irisin across albuminuria categories supports its potential role as a biomarker of nephropathy severity and aligns with meta-analytical evidence indicating that lower irisin levels are associated with advanced diabetic complications **Hou et al., (20); Wang et al., (21)**

Interestingly, while most studies report a negative correlation between irisin and renal impairment, some evidence suggests a compensatory increase in irisin in certain advanced cases, reflecting possible disease-stage–dependent regulation **Elesawy et al., (14)**

Circulating irisin showed significant negative correlations with glycemic indices, blood pressure, lipid parameters, albuminuria, and renal injury markers, while a strong positive correlation with eGFR was observed. These findings are further supported by the reports of **Hu et al. (11), Shelbaya et al. (13), and Khairallah et al. (16),** all of whom demonstrated that higher circulating irisin levels are consistently associated with better metabolic control and preserved renal function in patients with type 2 diabete

CONCLUSION In conclusion, our findings show that circulating irisin levels progressively decline with worsening diabetic nephropathy and increasing albuminuria in individuals with T2D. Lower irisin levels were strongly associated with poor glycemic control, dyslipidemia, elevated blood pressure, and impaired renal function, supporting its role as a biomarker for nephropathy severity. These findings suggest that irisin may reflect underlying metabolic and inflammatory disturbances contributing to renal injury.

RECOMMENDATIONS

Further longitudinal studies are needed to establish causality and to evaluate whether modulation of irisin could have therapeutic implications in the prevention or deterioration of diabetic nephropathy.

REFERENCES

1- Green, A., Hede, S. M., Patterson, C. C., Wild, S. H., Imperatore, G., Roglic, G., & Beran, D. (2021). Type 1 diabetes in 2017: global estimates of incident and prevalent cases in children and adults. Diabetologia, 64(12), 2741-2750.

2- Johansen, K. L., Chertow, G. M., Foley, R. N., Gilbertson, D. T., Herzog, C. A., Ishani, A., ... & Wetmore, J. B. (2021). US renal data system 2020 annual data report: epidemiology of kidney disease in the United States. American journal of kidney diseases, 77(4), A7-A8.

3- Zhu, H., Li, L., Liu, S., & Li, J. (2025). Smoking and diabetic nephropathy: An updated systematic review and meta-analysis. Journal of diabetes investigation, 16(3), 442-450.

4- Habas, E., Rayani, A., Habas, A., Farfar, K., Habas, E., Alarbi, K., ... & Alfitori, G. (2025). Advances in understanding and managing diabetic kidney disease: An updated review. Ukrainian Journal of Nephrology and Dialysis, (1 (85)), 66-80.

5- Lin, Y. C., Chang, Y. H., Yang, S. Y., Wu, K. D., & Chu, T. S. (2018). Update of pathophysiology and management of diabetic kidney disease. Journal of the formosan Medical Association, 117(8), 662-675.

6- Rasaratnam, N., Salim, A., Blackberry, I., Cooper, M. E., Magliano, D. J., van Wijngaarden, P., ... & Shaw, J. E. (2024). Urine albumin-creatinine ratio variability in people with type 2 diabetes: clinical and research implications. American Journal of Kidney Diseases, 84(1), 8-17.
7- Vistisen, D., Andersen, G. S., Hulman, A., Persson, F., Rossing, P., & Jørgensen, M. E. (2019). Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney function—even without albuminuria. Diabetes Care, 42(10), 1886-1894.
8- Grzeszczuk, M., Dzięgiel, P., & Nowińska, K. (2024). The role of FNDC5/Irisin in cardiovascular disease. *Cells*, *13*(3), 277.
9- Aboutorabi, R., Hariri, G., Khorasani, Z. M., & Mehrad-Majd, H. (2025). Relationship between serum irisin levels and renal function in patients with type 2 diabetes mellitus. *Caspian Journal of Internal Medicine*, *16*(3), 493.
10- Pillai, A., & Fulmali, D. (2023). A narrative review of new treatment options for diabetic nephropathy. *Cureus*, *15*(1), e33235.
11- Hu, W., Wang, R., Li, J., Zhang, J., & Wang, W. (2016). Association of irisin concentrations with the presence of diabetic nephropathy and retinopathy. *Annals of clinical biochemistry*, *53*(1), 67-74.
12- Liu, J. J., Liu, S., Wong, M. D., Tan, C. S., Tavintharan, S., Sum, C. F., & Lim, S. C. (2014). Relationship between circulating irisin, renal function and body composition in type 2 diabetes. *Journal of Diabetes and its Complications*, *28*(2), 208-213.
13- Shelbaya, S., Abu Shady, M. M., Nasr, M. S., Bekhet, M. M., Mageed, Y. A. A., & Abbas, M. (2018). Study of irisin hormone level in type 2 diabetic patients and patients with diabetic nephropathy. *Current diabetes reviews*, *14*(5), 481-486.
14- Elesawy, B. H., ASKARY, A. E., Mehanna, O. M., Elmorsy, E. A., Khalifa, M. M., Ali, S. E., & HAFEZ, A. A. E. (2025). High serum levels of irisin, visfatin and adiponectin as potential independent risk factors for diabetic nephropathy progression in patients with type 2 diabetes mellitus. *In Vivo*, *39*(3), 1615-1624.
15- El Haddad, H., Sedrak, H., Naguib, M., Yousief, E., Ibrahim, D. R., Abdel Samie, R. M., & Hamdy, A. (2019). Irisin level in type 2 diabetic patients and its relation to glycemic control and diabetic complications. *International Journal of Diabetes in Developing Countries*, *39*(4), 641-646.
16- Khairallah, M., K. Elshereef, H., S. Hassan, H., A. Dahpy, M., & A. Salah, A. (2025). Investigating irisin levels in patients with diabetic nephropathy: a cross-sectional study. *The Egyptian Journal of Internal Medicine*, *37*(1), 130.
17- Deng, Y., Shen, Y., Wu, Y., Wen, M., & Wang, F. (2025). Correlation of serum irisin levels with diabetic nephropathy: an exhaustive systematic appraisal and meta-analytical investigation. *Frontiers in Endocrinology*, *16*, 1599423.
18- Khidr, E. G., Ali, S. S., Elshafey, M. M., & Fawzy, O. A. (2017). Association of irisin and FNDC5 rs16835198 G> T gene polymorphism with type 2 diabetes mellitus and diabetic nephropathy. An Egyptian pilot study. *Gene*, *626*, 26-31.
19- Zhang, C., Ding, Z., Lv, G., Li, J., Zhou, P., & Zhang, J. (2016). Lower irisin level in patients with type 2 diabetes mellitus: A case-control study and meta-analysis. *Journal of diabetes*, *8*(1), 56–62.
20- Hou, Q., Song, R., Zhao, X., Yang, C., & Feng, Y. (2023). Lower circulating irisin levels in type 2 diabetes mellitus patients with chronic complications: A meta-analysis. Heliyon, 9(11).
21- Wang, R., & Liu, H. (2021). Association between serum irisin and diabetic nephropathy in patients with type 2 diabetes mellitus: a meta-analysis. Hormone and Metabolic Research, 53(05), 293-300.