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Original Article

The relationship of irisin, apelin-13, and immunological markers il-1α & amp, il-1β with diabetes in kidney failure patients

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Abstract

Chronic kidney disease (CKD) is often complicated by diabetes, impacting various biochemical and immunological markers. This study aimed to investigate the relationship between irisin, apelin-13, and immunological markers IL-1α and IL-1β in diabetic patients with CKD. This cross-sectional study was conducted from January to June 2023 in a tertiary care hospital in Tikrit City, Iraq. This study included 120 CKD patients and a control group including 20 healthy individuals. Patients were included in the study by convenience sampling method. Participants were evaluated using ELISA kits for irisin, apelin-13, and cytokines, with blood samples analyzed for relevant biochemical markers. Patients had irisin levels of 10.98 ± 2.5 ng/mL, significantly different from non-diabetic patients (12.40 ± 3.54 ng/mL) and controls (5.36 ± 1.06 ng/mL) ($p<0.001$). Apelin-13 was higher in diabetic patients (537.71 ± 124.78 pg/mL) compared to controls (181.26 ± 29.98 pg/mL) ($p<0.001$). IL-1α levels in diabetic patients were 715.30 ± 392.48 pg/mL, significantly higher than in control patients (206.27 ± 26.49 pg/mL) ($p<0.001$). IL-1β levels were 351.50 ± 81.82 pg/mL in diabetics, also higher than in control (145.79 ± 38.49 pg/mL) ($p<0.001$). The study highlights significant associations between biochemical markers and CKD in diabetic patients. Elevated levels of irisin, apelin-13, IL-1α, and IL-1β may serve as potential biomarkers for diabetes-related CKD complications.

Keywords: Chronic Kidney Disease, Cytokines, Diabetes Mellitus, ELISA

1. Introduction

Renal or kidney failure is a pathological condition in which the kidneys are unable to effectively eliminate waste materials and surplus fluids from the bloodstream. This may cause an accumulation of toxins in the body, leading to numerous systemic consequences [1]. The epidemiology of RF is alarming, with significant global prevalence. Approximately 850 million individuals worldwide are expected to be impacted by kidney disease, with the majority living in low-income and lower-middle-income countries (LICs and LMICs) [2]. The etiology of kidney failure is multifaceted, with diabetes mellitus, hypertension, glomerulonephritis and lifestyle-related factors such as obesity and smoking being the leading causes [3].

Diabetes, a chronic metabolic condition defined by high blood glucose levels, is the leading cause of kidney failure globally [4, 5]. Recent research has focused on the role of various biomarkers, such as irisin [6], apelin-13 [7], and immunological markers like interleukin-1 alpha (IL-1α) and interleukin-1 beta (IL-1β), in the pathophysiology of diabetes and kidney failure [8]. The immune markers IL-1α and IL-1β have been well investigated in a variety of inflammatory and autoimmune disorders and are essential elements of the inflammatory response. In kidney disease, these cytokines are believed to have a role in the persistent inflammatory condition that worsens kidney damage and hinders renal function [9].

Irisin is a myokine, a type of signaling molecule produced by muscles during exercise, derived from the proteolytic cleavage of the fibronectin type III domain-containing protein 5 (FNDC5) [10]. Studies have shown that Irisin has been implicated in glucose metabolism and insulin sensitivity [11], suggesting its potential role in diabetes and kidney disease management [6]. Additionally, Apelin-13, a peptide derived from the apelin prohormone, is another molecule of interest in the context of diabetes and kidney disease. This bioactive peptide has been shown to have diverse physiological effects, including regulation of blood pressure, fluid homeostasis, and glucose metabolism [12, 13]. A recent study by Gao et al. (2021), has indicated that apelin-13 may play a protective role in the kidneys, potentially mitigating some of the deleterious effects of diabetes on renal function [7].

Despite the growing body of research, there remain

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significant gaps in our understanding of how these biomarkers interact and contribute to the pathophysiology of diabetes in kidney failure patients. The novelty and necessity of the present study lies in its comprehensive approach to investigating these biomolecules in concert. Unlike previous research that has examined these factors separately, this study aimed to investigate the relationship between irisin, apelin-13, and immunological markers IL-1α and IL-1β in diabetic patients with CKD.

1. Materials and Methods

2.1. Study Design and Setting

This cross-sectional study was conducted for six months, from January to June 2023, at the Department of Nephrology, located in a tertiary care hospital in Tikrit City, Iraq.

2.2. Participants

The study included a total of 120 individuals diagnosed with CKD, comprising 44 men and 76 women aged between 40 and 60 years. An additional 20 healthy individuals formed the control group. Participants were recruited from the outpatient and inpatient facilities of the Nephrology Department. A convenience sampling method was employed, where eligible patients were approached and informed about the study. Once written informed consent was obtained, they were enrolled in the study.

Inclusion criteria involved patients aged > 18 years with a confirmed diagnosis of CKD, with or without diabetes, and who were willing to provide informed consent. Exclusion criteria included individuals with acute kidney injury, recent infections, active malignancies, or those who were pregnant, as these conditions could alter the study markers.

2.3. Data Collection

Data were collected through structured interviews, medical records, and laboratory analyses. Demographic information, medical history, and family history of diabetes were obtained via self-reported questionnaires.

Data collection involved both biochemical and immunological assessments. Blood samples were collected from all participants after obtaining informed consent. Samples were immediately processed or stored at -80°C for later analysis. The levels of irisin and apelin-13 were measured using ELISA kits provided by Elabscience (Germany), employing the Double Antibody Sandwich ELISA method for irisin and the Competitive ELISA approach for apelin-13. TNF-Alpha, Nesfatin-1, and PAI-1 levels were also evaluated using ELISA kits and sandwich ELISA method.

Blood urea levels were determined using a urease and glutamate dehydrogenase enzymatic method. Serum creatinine was measured using a creatininase and creatinase-based technique, as outlined by Cunningham et al. (2020) [14]. Blood glucose levels were assessed using the Hexokinase (HK) method, with the detection of NADH at 340 nm [15].

For the immunological markers, IL-1α and IL-1β levels were quantified using ELISA kits from R&D Systems (USA). The procedure involved a sandwich ELISA method, where microplates were coated with monoclonal antibodies specific to IL-1α and IL-1β. Serum samples were applied to these plates, followed by enzyme-linked antibodies. The intensity of color development, corresponding to cytokine concentration, was measured at 450 nm. Additional blood markers such as IL-6, IL-10, IL-17, IL-18, and IL-37 were also measured using similar ELISA techniques, ensuring comprehensive profiling of the inflammatory and immunological status of the participants.

2.4. Statistical Analysis

Data analysis was conducted using SPSS software, version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic data and biochemical markers. Continuous variables were expressed as means ± standard deviations, while categorical variables were expressed as frequencies and percentages. Differences between groups were analyzed using one-way ANOVA for continuous variables. A p-value of less than 0.05 was considered statistically significant.

2.5. Ethical Considerations

The Institutional Review Board (IRB) of XYZ University evaluated and granted approval to the research protocol. Prior to their involvement in the research, all individuals provided written informed permission. Participants were guaranteed the privacy of their data and their entitlement to uncompensated withdrawal from the research at any point without any consequences on their medical care.

3. Results

Table 1 shows the demographic distribution of patients. The results of sex distribution showed that 77 (64%) patients were female and 43 (36%) patients were male. Regarding the age distribution, the majority of participants were in the 50-55 age group, comprising 49 individuals (40.8%). This was followed by 38 (31.7%) participants aged between 40-50 years, and 33 (27.5%) participants aged over 56 years. Furthermore, a substantial portion of the participants reported having a family history of diabetes, with 74 (62%) individuals confirming this, whereas 46 (38%) participants reported no family history of the condition.

Table 2 presents the correlation between various bio-

Table 1. Demographic characteristics of patient participants (n = 120).

Variables		Number	Percentage
Sex	Male	43	36%
	Female	77	64%
Age	40-50	38	31.7%
	50-55	49	40.8%
	> 56	33	27.5%
Family History	Yes	74	62%
	No	46	38%

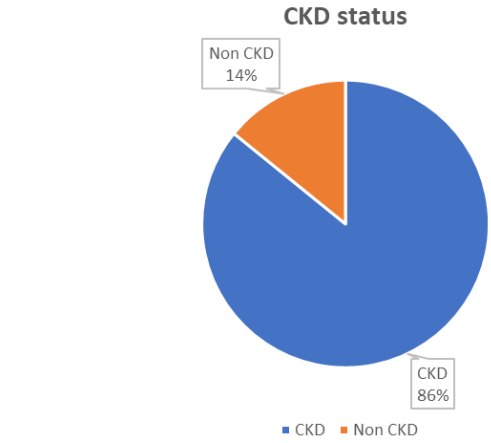

Fig. 1. Distribution of the DM Patients according to CKD status.

chemical markers for diabetic, non-diabetic, and control groups. For blood urea levels, the diabetic group had a mean value of 189.44 ± 80.71 mg/dL, the non-diabetic group had 184.66 ± 50.79 mg/dL, and the control group had a significantly lower mean of 25.88 ± 7.32 mg/dL ($p<0.001$). Serum creatinine levels were also significantly different among the groups, with diabetic patients showing a mean of 10.9 ± 2.62 mg/dL, non-diabetic patients 8.57 ± 4.15 mg/dL, and controls 0.68 ± 0.25 mg/dL ($p<0.001$). Glucose levels differed significantly between groups, where diabetic patients had a mean of 208.44 ± 96.58 mg/dL, non-diabetic patients 88.88 ± 12.28 mg/dL, and controls 102.33 ± 10.18 mg/dL ($p<0.001$). Albumin levels also showed statistical significance, with diabetic patients having 3.97 ± 0.91 g/dL, non-diabetic patients 4.52 ± 0.87 g/dL, and controls 3.56 ± 0.37 g/dL, yielding a p-value of 0.044.

The analysis of immunological markers in diabetic, non-diabetic, and control groups revealed significant differences in several parameters. In terms of IL-1α levels, diabetic patients had a mean of 715.30 ± 392.48 pg/mL, while non-diabetic patients displayed a higher mean of 921.72 ± 419.27 pg/mL; additionally, the control group demonstrated a show a mean of 206.27 ± 26.49 pg/mL ($p < 0.001$). Similarly, IL-1β levels were higher in non-diabetic patients, with a mean of 395.30 ± 133.93 pg/mL, compared to diabetic patients who had a mean of 351.50 ± 81.82 pg/mL. The control group again showed much lower levels, with a mean of 145.79 ± 38.49 pg/mL ($p < 0.001$). For the additional parameters, IL-6, IL-10, IL-17, IL-18, and IL-37, all were statistically significant ($p < 0.05$), except for IL-37 ($p = 0.60$) (Table 3).

Table 4 shows the relationship between immunoproteins in diabetic and non-diabetic patients and the control group. The levels of Apelin-13 in diabetic patients were 537.71 ± 124.78 pg/mL, whereas non-diabetic patients had slightly higher levels at 550.54 ± 138.71 pg/mL. Control subjects showed significantly lower levels, with a mean of 181.26 ± 29.98 pg/mL ($p<0.001$). For Irisin, diabetic patients had levels of 10.98 ± 2.5 ng/mL, compared to 12.40 ± 3.54 ng/mL in non-diabetics and 5.36 ± 1.06 ng/mL in controls ($p<0.001$). The other parameters, including PAI-1, Nesfatin-1, and TNF-Alpha, were also analyzed and

Table 2. Correlation between biochemical markers for patients.

	Blood Urea (mg/dL)	Serum Createnin (mg/dL)	Serum bilirubin (mg/dL)	Glucose (mg/dL)	Globulin (g/dL)	Total protein (g/dL)	Albumin (g/dL)	Calcium (mg/dL)
Diabetic	189.44 80.z71±	10.9 2.62±	0.72 0.82±	208.44 96.58±	2.96 0.81±	6.94 ± 0.88	3.97 ± 0.91	8.87 1.33±
Non diabetic	184.66 50.79±	8.57 ± 4.15	0.52 0.28±	88.88 12.28±	2.96 1.16±	7.48 ± 1.51	4.52 ± 0.87	8.58 1.31±
Control	25.88 7.32±	0.68 ± 0.25	0.68 ± 0.20	102.33 ± 10.18	3.28 ± 0.81	6.85 ± 0.65	3.56 ± 0.37	8.64 0.27 ±
f-test	25.56	31.90	0.38	12.08	0.34	0.90	3.55	0.17
p-value	<0.001	<0.001	0.68	<0.001	0.7	0.41	0.044	0.83

Table 3. Correlation between immunological markers.

	IL-1α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)	IL-17 (pg/mL)	IL-18 (pg/mL)	IL-37 (pg/mL)
Diabetic	715.30 ± 392.48	351.50 ± 81.82	34.22 ± 10.97	46.57 ± 18.14	517.01 ± 132.1	563.21 ± 104.99	379.75 ± 134.24
Non diabetic	921.72 ± 419.27	395.30 ± 133.93	36.29 ± 12.13	47.48 ± 14.06	539.24 ± 139.76	588.50 ± 346.16	441.14 ± 172.08
Control	206.27 ± 26.49	145.79 ± 38.49	8.83 ± 1.81	7.74 ± 3.26	178.95 ± 30.43	265.70 ± 118.34	491.08 ± 342.46
f-test	11.07	18.34	23.29	25.82	29.02	6.006	0.50
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.60

Table 4. Correlation between immunoproteins of diabetic patients.

	Apelin-13 (pg/mL)	PAI-1 (ng/mL)	Irisin (ng/mL)	Nesfatin-1 (ng/mL)	TNF-Alpha (pg/mL)
Diabetic	537.71 ±124.78	21.06 ±5.79	10.98 ± 2.59	370.06 ± 99.26	231.44 ± 56.39
Non diabetic	550.54 ±138.71	22.90 ±7.11	12.40 ±3.54	374.45 ±125.06	236.99 ±68.35
Control	181.26 ±29.98	8.52 ±1.16	5.36 ±1.06	198.05 ±26.85	92.97 ±14.56
f-test	33.21	19.32	18.38	10.42	22.28
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

found to be statistically significant ($p<0.001$).

4. Discussion

This study aimed to examine the relationship between irisin, apelin-13, and the immunological markers IL-1α and IL-1β in diabetic patients with CKD. The present study found significant differences in biochemical markers, immunological markers, and immunoproteins among diabetic, non-diabetic, and control groups. Specifically, diabetic patients exhibited elevated levels of blood urea, serum creatinine, glucose, and inflammatory cytokines, also irisin and apelin-13 levels were higher in diabetic patients compared to controls.

In terms of CKD status among diabetic patients, the study found a high prevalence of CKD, which aligns with the findings of Wang et al. (2020), who reported that CKD is a common complication in diabetic patients due to prolonged hyperglycemia and hypertension [16]. Similarly, a study by Kumar et al. (2023) supports the notion that diabetes significantly contributes to the progression of CKD, highlighting the importance of early detection and management [5]. However, the study by Erfanpoor et al. (2021) did not show any synergistic effect between diabetes and hypertension on the incidence of CKD, and this difference in results may be due to methodology and ethnic differences, which requires further studies in this field [17].

The findings regarding irisin align with previous studies highlighting its role as a biomarker for metabolic disturbances in diabetic patients. A study by Huh et al. (2016) demonstrated elevated irisin levels in diabetic patients, suggesting a compensatory mechanism in response to metabolic stress [18]. Similarly, a study by He et al. (2021) corroborated these findings, noting that increased irisin levels might contribute to improved glucose homeostasis in diabetic patients [19]. However, conflicting results were reported by Hwang et al. (2016) [20], Zhang et al. (2016) [21], and Elizondo et al. (2019) [22]. The results of their study showed that circulating irisin levels in diabetic patients are lower than in those without diabetes, suggesting that variations in study design and patient characteristics could account for these discrepancies.

Apelin-13's role in diabetes has been a subject of interest, with previous research indicating its involvement in glucose metabolism and insulin sensitivity. The current study's findings of elevated apelin-13 levels in diabetic patients are consistent with results from studies by Cui et al. (2024) [23], and Mehri et al. (2023), which reported increased apelin-13 in the context of hyperglycemia and insulin resistance [24]. In addition, the results showed that the levels of PAI-1 [25], and TNF-Alpha [26], are also increased in CKD diabetic patients, which is in line with the results of previous studies. Unlike the present study, where Nesfatin-1 levels were increased in diabetic patients, studies conducted by Liu et al. (2014) [27], and Khalil et al. (2024) [28], reported a decrease in this factor in diabetic patients. This inconsistency of the results is due to the difference in the methodology of the studies because these two studies were not conducted on CKD patients with diabetes.

The immunological markers IL-1α and IL-1β were also significantly elevated in diabetic patients, consistent with the literature identifying these cytokines as key players in the inflammatory response associated with diabetes. The study's outcomes are in line with research by Galozzi et al. (2021), which highlighted the role of IL-1 cytokines in the pathophysiology of diabetes [29]. Similarly, Alfadul et al. (2022) found that higher IL-1β levels were associated with increased risk of type 2 diabetes [30]. In addition, the results showed that the levels of IL-6, IL-10, IL-17, and IL-18 are also increased in CKD diabetic patients, which is in line with the results of previous studies [31–33].

5. Conclusion

In conclusion, the study underscores the complex interplay between metabolic, inflammatory, and renal factors in diabetic patients with CKD. The elevated levels of irisin, apelin-13, IL-1α, and IL-1β in diabetic patients may reflect compensatory mechanisms and inflammatory responses associated with diabetes and its complications. The alignment with previous studies supports the potential utility of these biomarkers in diabetic patient management, although discrepancies highlight the need for further research to clarify these relationships.

Conflict of interest

The authors affirm that there are no conflicts of interest in relation to the publishing of this work.

Consent for publications

The authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Informed Consent

Once written informed consent was obtained, they were enrolled in the study.

Availability of data and material

The corresponding author may provide the quantitative data of the research upon a fair request.

Authors' contributions

The authors contributed equally to this research study.

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