Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
10.34172/jkmu.2884
JKMU. 2025;32:2884

Original Article

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Evaluation of the Relationship between Serum ACTH and Uric Acid Levels and Insulin Resistance in Patients with Type 2 Diabetes

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Abstract

Background: Research indicates that high levels of uric acid (UA) are linked to insulin resistance (IR), which may elevate the risk of diabetes development. Adrenocorticotropic hormone (ACTH) regulates cortisol, a hormone essential for glucose metabolism. This study examined the relationship between ACTH, uric acid (UA) levels, and IR in diabetic patients.

Methods: This case-control study involved thirty individuals with type 2 diabetes (T2D) and 30 healthy controls (45% male and 55% female) in Iran. Demographic data were collected, and serum levels of ACTH and insulin were assessed using ELISA; serum UA levels were measured through spectrophotometry. The data were analyzed using SPSS version 24.

Results: Significant differences were observed in body mass index (BMI), fasting blood sugar (FBS), HbA1c, and IR, with higher mean values in the T2D group compared to the control group ($P<0.05$). UA levels were significantly elevated in all patients ($P=0.004$), particularly males ($P=0.009$), compared to controls. Moreover, increased UA levels were linked to greater disease risk ($P=0.007$). ACTH levels were also significantly higher in T2D individuals than in healthy individuals ($P<0.001$), and elevated ACTH levels correlated with an increased disease risk ($P=0.002$). Additionally, the relationship between ACTH and UA levels and IR in the T2D group was significant compared to the control group.

Conclusion: The findings indicate a relationship between ACTH, UA, IR, and T2D, suggesting that these factors may serve as important indicators for diagnosing the progression of the disease.

Keywords: Adrenocorticotropic hormone, Uric acid, Insulin resistance, Diabetes mellitus

Citation: Oraibi Hasan Matrood A, Hamidi Alamdari D, Homayouni Tabrizi M, Pouresmaeil V. Evaluation of the relationship between serum ACTH and uric acid levels and insulin resistance in patients with type 2 diabetes. *Journal of Kerman University of Medical Sciences*. 2025;32:2884. doi:10.34172/jkmu.2884

Received: May 15, 2021, **Accepted**: March 25, 2025, **ePublished**: April 7, 2025

Introduction

Diabetes mellitus (DM) refers to various metabolic disorders characterized by abnormally high blood sugar levels caused by difficulties in insulin production, its performance, or a mix of both issues. Persistent high blood sugar associated with diabetes can cause damage and dysfunction in various organs over time, particularly affecting the eyes, kidneys, nerves, heart, and blood vessels. Type 2 diabetes (T2D) impacts about 3% of the global population, which translates to roughly 100 million people worldwide. The incidence of T2D is notably higher in Europe and the USA, where it affects 5%–7% of the population, with a rising trend. While the exact causes of T2D are not fully understood, a major contributing factor is the complex interaction of genetic and environmental elements, including obesity, unhealthy eating habits, and lack of physical activity. T2D represents over 90% of all diabetes cases and is linked to both microvascular and macrovascular complications (1).

Adrenocorticotropic hormone (ACTH), produced in the anterior pituitary gland, prompts the adrenal cortex to discharge cortisol and aldosterone (2-5). Cortisol, an essential glucocorticoid, is crucial for glucose metabolism and the body's stress response (6). It also regulates the activities of the hypothalamus, pituitary gland, and adrenal glands. Upon a decrease in cortisol levels, the hypothalamus initiates the release of corticotropin-releasing hormone (CRH), subsequently stimulating the pituitary gland to discharge ACTH, resulting in a rise in cortisol levels (7-9). Monitoring ACTH levels is vital for assessing changes in blood cortisol and diagnosing hormonal disorders related to adrenal or pituitary issues (10). As mentioned,

cortisol, the most recognized glucocorticoid in the body, has various functions, including reducing inflammation, modulating immune responses, affecting metabolism, and raising blood sugar levels (11-16).

Many studies have revealed that cortisol can affect metabolism and lead to high blood sugar levels, which might be pertinent to the development of insulin resistance (IR) and DM (17-20). This research aimed to investigate the connection between serum ACTH and UA levels in individuals with T2D and those without diabetes to understand their role in IR and the disease itself.

Methods

Participant

The study included 30 patients diagnosed with T2D by an endocrinologist who were referred to Mashhad University Hospitals in 2020. A control group of 30 healthy individuals was also recruited.

The inclusion criteria for the patients were being over 25 years old, having a confirmed diagnosis of T2D, and not having heart disease or diabetic nephropathy. The control group consisted of individuals over 25 years old with no history of heart disease, T2D, or diabetic nephropathy.

Exclusion criteria included current pregnancy, liver or kidney disease, hypothyroidism, hyperthyroidism, acute coronary syndromes, cancer, or the use of vitamin supplements.

All participants provided their informed written consent for this study.

Procedure

Data on anthropometric variables (height, weight, and body mass index [BMI]), demographic information (FBS, HbA1c, total cholesterol, HDL, LDL, triglycerides, and systolic and diastolic pressure), and medication history were collected from patient records at the hospital. For additional tests, 5 ml blood samples were drawn from each participant to measure UA, ACTH, and insulin levels. The samples were centrifuged at 10,000 rpm for 5 minutes to separate the serum, which was then stored at -20 °C until analysis.

The ACTH hormone was measured using the Elabscience ELISA kit (Catalog No.: E-EL-H0137) (21). The testing procedure involved transferring 50 µL of samples and standards to the wells, adding 50 µL of biotinylated detection antibody working solution, covering the kit, and incubating it at 37 °C for 45 minutes. The wells were emptied and washed thrice with 350 µL of washing buffer. Following this, 100 µL of the enzyme horseradish peroxidase (HRP) conjugate was added, and the mixture was incubated for 30 minutes at 37 °C. The wells were rinsed again with washing buffer, and 90 µL of substrate reagent was added, followed by a 15-minute incubation at 37 °C. Finally, 50 µL of stop solution was added, and the resulting color was measured at a wavelength of 450 nm.

Serum insulin levels were evaluated according to the protocol for the Human insulin ELISA kit (Abcam), and the IR was calculated according to the HOMA-IR formula (22).

$$HOMA\text{-}IR = [IF\ (\mu U/mL) \times GF\ (mmol/L)] / 22.5$$

Here, IF and GF denote fasting insulin and fasting glucose, respectively.

The serum levels of UA and creatinine were determined using spectrophotometry following the manufacturer's kit protocol.

Statistical methods

Data were displayed in tables alongside relevant statistical metrics, such as the mean ± standard deviation. The study data were analyzed using SPSS version 24. Various statistical tests were employed, including chi-square (χ^2) tests, logistic regression for assessing disease risk, Mann-Whitney U test for non-normally distributed data, *t*-tests, and analysis of variance (ANOVA). The statistical significance level was set at $P < 0.05$.

Results

Among the diabetic patients (30 with an average age of 48.0 ± 4.5 years) in this study, 13 were male, and 17 were female. The control group included 30 healthy people (with an average age of 46.0 ± 5.7 years), of whom 14 were male and 16 were female. No significant difference was observed in the sexes ($P = 0.795$) and age ($P = 0.180$) between the control and T2D groups. According to the results, diabetic individuals and control samples had significant differences in weight ($P = 0.013$), BMI ($P = 0.009$), FBS ($P < 0.001$), and HbA1c ($P < 0.001$). These parameters were higher in diabetic patients (Table 1). In terms of cholesterol, LDL, HDL, triglycerides, creatinine, and blood pressure, there was no significant difference between the two groups (Table 1). Only the mean creatinine levels in male patients were significantly higher than that of the males in the control group ($t = 2.49$, $df = 5$, $P = 0.02$; $Z = 2.37$, $P = 0.018$). According to Figure 1, the mean UA level for diabetic patients is 6.59 ± 1.14 mg/dL, while for healthy individuals it is 5.77 ± 0.94 mg/dL ($t = 3.04$, $df = 58$, $P = 0.004$). Also, due to the difference in normal rates between males and females, the mean equality test was evaluated separately in these two groups. It was found that UA levels in females were not significantly different between patients and controls. However, male patients had an average UA level of 6.75 ± 1.05 mg/dL versus 5.65 ± 0.94 mg/dL in the 14 healthy individuals. The results in males showed that the mean UA in patients was higher than in the control group ($t = 2.85$, $df = 25$, $P = 0.009$, $Z = 2.41$). Also, the results showed that increased UA increases the risk of disease (OR = 2.13, $P = 0.007$) (Table 2).

Table 1. Comparison of blood indices between diabetic patients and control groups

Risk factor	Diabetic patients (mean ± standard deviation)	Control (mean ± standard deviation)	*P* value	95% CI	OR
Weight (kg)	85.5 ± 11.65	75.83 ± 15.77	0.013	1.1–01.09	1.05
Height (cm)	170.43 ± 8.5	169.07 ± 10.3	0.570	0.1–96.07	1.02
BMI (kg/m²)	29.58 ± 4.62	26.34 ± 3.77	0.009	1.1–05.40	1.21
FBS (mg/dL)	133..13 ± 16.14	95.93 ± 16.42	<0.001	1.1–07.22	1.14
HbA1c (%)	7.64 ± 0.64	5.02 ± 0.56	<0.001	2.1–2.71	1.06
Total Chol. (mg/dL)	189.2 ± 53.49	177.6 ± 50.27	0.385	0.1–99.01	1
HDL (mg/L)	45.13 ± 19.28	43.37 ± 19.28	0685	0.1–98.04	1.01
LDL (mg/dL)	106.32 ± 37.11	102.7 ± 35.38	0.707	0.1–99.02	1
TG (mg/dL)	163.93 ± 89.7	163.43 ± 66.27	0.980	0.1–99.01	1
Creatinine (mg/dL)	1.57 ± 0.66	1.38 ± 0.61	0.267	0.3–7.68	1.6
Systolic pressure (mm Hg)	137.1 ± 9.9	130.67 ± 16.17	0.072	1.1–00.8	1.04
Diastolic pressure (mm Hg)	86.93 ± 10.39	89 ± 14.7	0.525	0.1–95.03	0.99

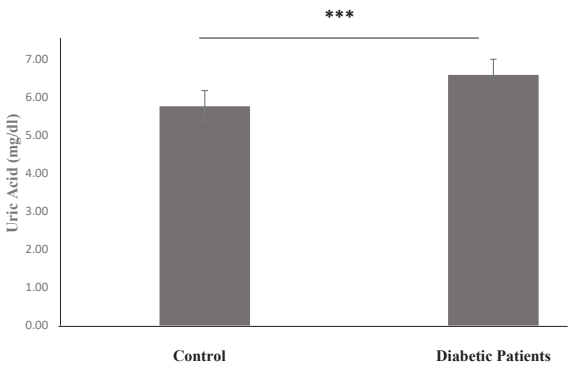

Figure 1. Distribution of uric acid (mg/dL) in patients with type 2 diabetes and control group (*P* = 0.004)

Conversely, the mean level of ACTH in diabetic patients was 12.87 ± 4.43 ng/mL compared to the control group's 4.53 ± 1.63 ng /mL. According to Figure 2, the mean level of ACTH hormone in the patient group was significantly higher than in the control group ($t = 9.67$, $df = 58$, $P = 0.002$; $Z = 6.59$).

Figure 3 presents the IR results in diabetic patients and healthy subjects. The IR value in patients was 3.56 ± 3.86; however, for healthy subjects, it was 0.84 ± 0.57 ($P = 0.001$).

Using logistic regression, we examined the role of risk factors in disease development. The results are presented in Table 1. The results showed that increased BMI, FBS, and HbA1c increase the disease risk ($P < 0.05$). Also, we examined the role of ACTH and UA in causing disease using logistic regression. The results presented in Table 2 show that increased ACTH or UA levels increase the risk of disease ($P = 0.002$; $P = 0.007$, respectively). Finally, the relationship between IR and UA, as well as between IR and ACTH, is presented in Table 3. According to these results, in the patient group, UA and ACTH significantly affected IR ($R = 0.326$, $p = 0.011$), ($R = 0.101$, $P = 0.014$), respectively.

Table 4 presents the correlation between ACTH and UA. The results showed a significant correlation between the two parameters in the diabetic group ($P = 0.002$).

Discussion

This case-control study included 60 participants comprising 30 individuals diagnosed with T2D in the case group and 30 healthy individuals in the control group. There were no significant variations in gender or age between the two cohorts, and the risk of diabetes was comparable for both male and female individuals. The results demonstrated notable variations between the groups regarding BMI, FBS, HbA1c, and insulin concentrations, with diabetic participants exhibiting higher mean values than the control group. These results have been confirmed by other studies (23-25). However, no significant differences were observed in lipid profiles, creatinine levels, or blood pressure between the groups, which is in contrast with our earlier research on systolic blood pressure (26) and with other studies in terms of lipid profiles (27,28). In these studies, the population included individuals with hypertension, which may account for these discrepancies. Nevertheless, our previous research and other studies (23,25) found no significant differences in lipid profiles, consistent with the present study, suggesting that the differences observed in other research may be attributed to the heterogeneity of the populations studied.

ACTH regulates cortisol and aldosterone secretion from the adrenal cortex. Our results show that diabetic patients have significantly higher mean IR values and ACTH levels than control subjects, indicating that ACTH significantly influences IR.

Bakov and Milanov conducted a study with 355 diabetic patients to assess blood ACTH levels using the radioimmunoassay method. They found significantly elevated ACTH levels in diabetic patients compared to healthy controls, which aligns with our findings. The authors concluded that effective diabetes management

Table 2. Comparison of uric acid and ACTH hormone between diabetic and control groups

Risk factors	Patient (mean ± standard deviation)	Control (mean ± standard deviation)	*P* value	95% CI	OR
Uric acid male (mg/dL)	6.75 ± 1.05	5.65 ± 0.94	0.009	1.05–1.40	1.99
Uric acid female (mg/dL)	5.75 ± 0.65	5.87 ± 0.96	0.085	-0.71–0.47	1.37
Uric acid (mg/dL)	6.59 ± 1.14	5.77 ± 0.94	0.004	1.3–23.67	2.13
ACTH (ng/mL)	12.87 ± 4.43	4.53 ± 1.63	0.002	1.7–55.31	3.37

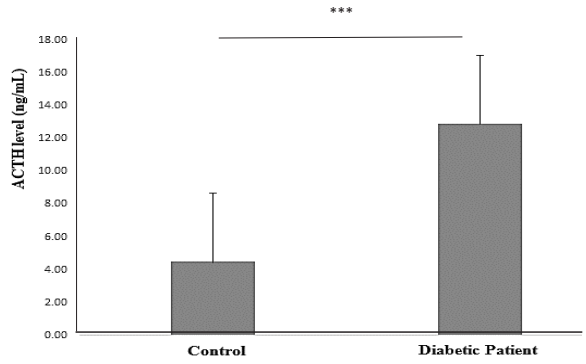

Figure 2. Distribution of ACTH hormone (ng/mL) in patients with type 2 diabetes and control group (*P* = 0.002)

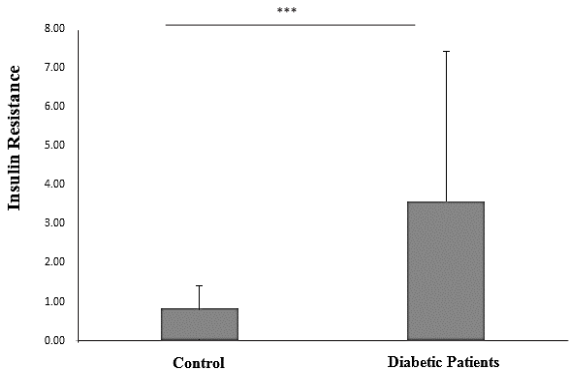

Figure 3. Distribution of insulin resistance in patients (HOMA-IR) with type 2 diabetes and control group (*P* = 0.001)

helps normalize ACTH levels (29).

Research has shown that when UA levels in the blood rise above normal, it can lead to an acidic environment in the body's fluids, negatively impacting cell function and potentially resulting in metabolic diseases over time. High UA levels trigger various pathophysiological changes through processes like inflammation, oxidative stress, and damage to blood vessel linings, which can facilitate the development and advancement of multiple diseases. Our findings revealed that, in males and overall (but not in females), diabetic patients had significantly higher average UA levels compared to the control group. Additionally, an increase in UA levels correlates with a higher disease risk. Some studies have shown that UA is significantly associated with diabetes (30,31).

Bombelli et al found that an increase in UA leads to an increased risk of impaired fasting glucose (IFG), and people with higher median UA levels may also develop metabolic syndrome and diabetes (32). It has been proposed as a possible mechanism that UA directly inhibits the trigger of the insulin signaling pathway by enzyme recruitment at insulin receptors (33).

Yokoyama et al examined the hypothalamic-pituitary-adrenal (HPA) dysfunction and IR in patients with depression. Their study, which included 15 elderly patients with depression and 17 elderly controls, revealed that HPA axis disorders are linked to IR and the severity of the disease (34). This confirms the results obtained in our study regarding the increase in ACTH hormone levels in diabetic patients and its relationship with IR and disease. Additionally, Oltmanns et al examined the relationship between diabetes-related metabolic disorders and cortisol concentrations in patients with T2D. This study was performed on 190 patients with T2D and showed that the clinical severity of T2D was directly related to cortisol concentration. In addition, the results showed evidence of a positive relationship between metabolic disorders and cortisol levels (35). Muscogiuri et al investigated the occurrence of IR in individuals with adrenal insufficiency. The results of this experiment, which was performed on 40 samples of people with adrenal secretion disorders, showed that adrenal disorders are related to IR in patients and with the progression of the disease (36).

Increased ACTH levels may lead to higher cortisol secretion, which can impact metabolism and result in hyperglycemia, potentially contributing to the development of IR in T2D. Conversely, elevated serum UA levels have been reported to predict the onset of T2D (37), and serum UA concentration independently correlates with IR (38), which was confirmed by our study's findings.

Nevertheless, the actual mechanism of action of ACTH and UA on IR or disease progression is still not completely understood.

Conclusion

This study examined the serum concentrations of ACTH and UA in individuals diagnosed with T2D in comparison to a control group of healthy individuals. We also investigated the correlation between these levels

Table 3. Correlation between insulin resistance and uric acid and ACTH

Variable	Control		Diabetes	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
Uric acid	0.188	0.321	0.326	0.011
ACTH	0.027	0.444	0.101	0.014

Table 4. Correlation between ACTH and uric acid

Group	Variable	Value
Control	Correlation coefficient	0.355
	P value	0.054
Diabetic patient	Correlation coefficient	0.540
	P value	0.002

and IR. The findings suggested a significant association between IR and the average levels of ACTH and UA in both genders. Moreover, the findings indicated that elevated serum levels of ACTH or UA are associated with an increased susceptibility to developing the condition. Monitoring these parameters could be a valuable strategy for preventing and managing type 2 diabetes in patients.

Acknowledgements
The authors express their gratitude to all colleagues at Islamic Azad University, Mashhad branch, for their help and support in this work and to colleagues at Mashhad University hospitals.

Authors' Contribution
Conceptualization: Vahid Pouresmaeil, Daryoush Hamidi Alamdari.
Data curation: Amjed Oraibi Hasan Matrood, Masoud Homayouni Tabrizi
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Investigation: All authors.
Methodology: All authors.
Supervision: Daryoush Hamidi Alamdari, Vahid Pouresmaeil.
Validation: All authors.
Visualization: All authors.
Writing–original draft: Vahid Pouresmaeil, Masoud Homayouni Tabrizi.

Competing Interests
The authors declare no conflict of interest.

Ethical Approval
The local Ethics Committee affiliated with the Islamic Azad University, Mashhad Branch (Medical Sciences), approved this study (Registration Code: IR.IAU.MSHD.REC.1396.112).

Funding
This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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