Turkish Journal of Health Science and Life

Serum and urine adropin levels following urinary microalbuminuria in patients with type 2 diabetes

Burak Öz[a*], Ahmet Karataş[b], Kader Uğur[c], Süleyman Aydın[d] ,Nevzat Gözel[e]

[a, b] *Firat University, Medical Faculty, Rheumatology Department, Elazig, Türkiye*

[c] *Firat University, Medical Faculty, Endocrinology Department, Elazig, Türkiye*

[d] *Firat University, Medical Faculty, Biochemistry Department, Elazig, Türkiye*

[e] *Firat University, Medical Faculty, Internal Medicine Department, Elaziğ, Türkiye*

ARTICLE INFO

RESEARCH ARTICLE

Article history:

Received: 30 October 2024

Accepted: 24 December 2024

Available : 31 December 2024

[a] https://orcid.org/0000-0001-9762-2401

[b] https://orcid.org/0000-0002-6725-4182

[c] https://orcid.org/0000-0003-4028-2041

[d] https://orcid.org/0000-0001-6162-3250

[e] https://orcid.org/0000-0001-7326-6860

*Correspondence: Burak ÖZ

Firat University Medical Faculty Rheumatology Department

e-mail: burak23oz@hotmail.com

Turkish Journal of Health Science and Life

2024, Vol.7, No.3, 96-104.

DOI: https://10.56150/tjhsl.1575803

ABSTRACT

Objective: Diabetes mellitus disrupts energy balance due to insulin deficiency or resistance, presenting a significant public health challenge. A major complication is end-stage renal disease (ESRD), primarily resulting from diabetic nephropathy. Peptide hormones significantly contribute to the pathogenesis of diabetes. Adropin, a peptide hormone associated with energy regulation, has an unclear relationship with diabetes and nephropathy. This study aims to evaluate serum and urinary adropin levels in diabetic patients and explore the correlation between these levels and diabetic nephropathy occurrence.

Materials and Methods: In this cross-sectional study, serum and urine adropin levels were measured via enzyme-linked immunosorbent assay (ELISA) in 60 diabetic patients categorized by normoalbuminuria, microalbuminuria, and overt albuminuria, alongside 20 healthy controls.

Results: Serum adropin levels were significantly lower in healthy controls, normoalbuminuric, and microalbuminuric groups compared to the overt albuminuric group ($p=0.007$, $p<0.001$, $p=0.008$). Adropin positively correlated with serum creatinine and microalbuminuria levels ($p=0.031$, $r=0.242$; $p=0.001$, $r=0.379$). Urinary adropin levels were significantly higher in diabetic patients than in controls ($p=0.001$) and lower in the microalbuminuric group compared to both normoalbuminuric and overt albuminuric groups ($p=0.026$ for both).

Conclusion: Adropin levels are significantly altered in diabetic nephropathy, highlighting its potential as both a biomarker and a therapeutic target due to its involvement in insulin sensitivity, inflammation, and metabolic pathways. Future research should investigate the mechanisms through which adropin influences renal function and its therapeutic potential in metabolic disorders, especially in diabetic kidney disease, while also addressing the implications of adropin resistance.

Keywords: Adropin, diabetes mellitus, diabetic nephropathy.

1. INTRODUCTION

Diabetes represents a significant global health concern, ranking as one of the most prevalent causes of diminished quality of life and untimely death worldwide. It is a growing epidemic, driven by current dietary habits and sedentary lifestyles (1). The subclinical and unrecognised nature of chronic hyperglycaemia results in the development of significant chronic complications(2).

Diabetic nephropathy (DN) is a prevalent and severe complication of diabetes, with significant associations with heightened morbidity and mortality risks in patients. In general, there appears to be an increase in the prevalence of diabetic nephropathy (DN) in correlation with the growing number of individuals with diabetes. Consequently, DN stands as one of the most significant causes of end-stage renal failure (ESRD) (3). Diabetic nephropathy (DN) develops over time following a latent period and affects approximately one-third of diabetic patients. Although it is not advisable to solely monitor the progression of this disease by focusing on proteinuria levels, microalbuminuria continues to represent a valuable indicator in this regard. The affected

population exhibits advanced glomerulopathy even at the microalbuminuria stage (4). Appropriate treatment and risk management can facilitate the achievement of normoalbuminuria in microalbuminuric patients (5). It is noteworthy that there are also patients with diabetic nephropathy (DN) who do not exhibit albuminuria, which presents a challenge for the accurate diagnosis and management of the disease (6). Furthermore, the complexity and poorly understood nature of the disease have resulted in the inability to achieve effective and adequate treatment thus far.

Adropin is a 76-amino acid peptide that is expressed in a multitude of different tissues and organs, including the kidney. Adropin, encoded by the Enho gene, has been demonstrated to exert significant effects on energy homeostasis (7). It exerts effects on insulin signalling pathways, including a reduction in hepatic glucose production, and exerts effects on insulin resistance. Moreover, it has been demonstrated to positively impact lipid levels. Adropin is implicated in the resolution of inflammation at the tissue level, acting as an inhibitor of the pro-inflammatory cytokines TNF-α and IL-6. It has been demonstrated that adropin exerts angioprotective effects by enhancing the production of endothelial nitric oxide synthase (8, 9).

2. MATERIALS AND METHODS

2.1 Sample of the Research

A total of 60 participants with normoalbuminuric, microalbuminuric and overt albuminuria according to microalbumin level calculated in spot urine from type 2 diabetic patients who had presented themselves at endocrinology polyclinic, and 20 healthy controls, were included in the study.

Individuals with type 1 DM, urinary tract infection, end -stage chronic renal failure, liver cirrhosis, congestive heart failure, chronic obstructive pulmonary disease, malignancy and known chronic systemic diseases were excluded from participation.

The characteristics of the participants in terms of their social and demographic profiles were documented, as were the biochemical parameters (AST, ALT, LDL cholesterol, triglyceride level, HbA1c, LDL cholesterol, triglyceride level, urinary microalbuminuria level) and any drug treatments. This simultaneous recording was conducted from the patient files.

2.2 Laboratory analysis and data collection

In the context of routine admission, 5ml blood samples and simultaneous urine samples were collected from the patients for the purpose of determining their blood and urine adropin levels. This was done after the patients had fasted for a period of 8-10 hours, and only once. The blood samples were subjected to centrifugation under conditions and methods appropriate for the separation of serum. The serum and urine samples were stored in Eppendorf tubes in a deep freezer at -30˚C for subsequent analysis of adropin levels in both biological fluids.

The adropin levels in urine and serum were determined by the Eliza method, employing commercially available kits (Human Adropin 34-76, Phoenix Pharmaceutics, Inc.). Code: The EK-032-35 (Lot no: 604526, USA) was utilised with the Eliza Device (ELX 800), in accordance with the specifications outlined in the manufacturer's catalogue.

2.3 Statistical analyses

The data were subjected to descriptive and inferential statistical analysis using the Statistical Package for the Social Sciences (SPSS 18.0, Chicago, IL, USA). Resultant data were presented as mean ± standard deviation. The Kolmogorov-Smirnov test was employed to assess the distributional normality of the data. In instances where the data did not exhibit normal distribution characteristics, logarithmic transformations were applied prior to statistical evaluation. The numerical data were subjected to Kruskal-Wallis or Mann-Whitney U tests for comparison, while the non-numerical data were evaluated using chi-square tests. Correlation analyses were conducted using Pearson's test. A p-value of less than 0.05 was regarded as indicative of statistical significance.

2.4 Ethical Issues in Research

The study was conducted in accordance with the ethical standards set forth by the Fırat University

Faculty of Medicine Clinical Studies Ethics Committee (97521439-110/13-02-03). The participants in both the experimental and control groups were briefed on the nature of the study and provided written informed consent prior to their enrolling in the study.

3. RESULT AND DISCUSSION

3.1 Results

The sociodemographic and routine laboratory data, along with the statistical comparisons among the aforementioned research groups, are illustrated in Table 1. The control group exhibited a younger mean age and lower BMI, LBW, BACC, HbA1c, and microalbuminuria levels compared to the study groups. The creatinine level in the overt albuminuria group was found to be notably heightened in comparison to the control and other study groups. The age at which diabetes was first diagnosed in the overt albuminuria group was found to be older in comparison to the other subjects included in the study. Furthermore, the mean age of patients with microalbuminuria was higher than that of patients with normoalbuminuria. The study groups exhibited elevated levels of low-density lipoprotein cholesterol in comparative analysis with the control group.

Table 2 presents the number of subjects in each study group and the statistical comparisons made in terms of hypertension, obesity and drug use. The prevalence of hypertension was higher in the overt and microalbuminuria groups than in the diabetic patients without albuminuria (p=0.004). Furthermore, a higher proportion of these patients were using ACE inhibitors or angiotensin receptor blockers (p=0.001). No discernible statistical distinction was identified in HbA1c levels among the DM patient cohorts. The use of metformin decreased with increasing microalbuminuria class, with the lowest rate observed in the group with overt albuminuria ($p < 0.001$). A comparable pattern was identified with regards to the utilization of non-metformin oral antidiabetic (OAD) medications (p= 0.015). In contrast to the use of OADs, the use of insulin increased with increasing albuminuria class (p=0.004). No notable discrepancies were identified between the groups with respect to insulin treatment type and obesity status.

Table 1: Sociodemographic characteristics and routine laboratory data in the study groups

	Control (n=20)	Normo albuminuria (n=20)	Micro albuminuria (n=20)	Overt albuminuria (n=20)	p *
Percentage of women (%)	50	60	65	35	0,240**
Age (years)	47,3 ± 9,5	58,0 ± 9,4××	59,5 ± 9,3 ××	59,0 ± 9,1××	< 0,001
DM age (years)	0	6,4 ± 4,8	11,5 ± 4,4 ↑↑	19,25 ± 5,8 ↑↑↑ †††	< 0,001
BMI (kg/m²)	24,1 ± 1,1	28,1 ± 4,3××	29,6 ± 4,6 ×××	27,3 ± 3,5 ×××	< 0,001
Fbg (mg/dL)	93,1 ± 3,3	151,4±43,0 ×××	164,1 ± 36,9 ×××	158,7 ± 31,0 ×××	< 0,001
Pbg (mg/dL)	122,2 ± 11,1	256,5±93,5 ×××	304,4 ± 81,4 ×××	263,5 ± 64,6 ×××	< 0,001
HbA1c (%)	5,0 ± 0,3	8,3 ± 2,6×××	9,3 ± 2,0 ×××	8,8 ± 1,3 ×××	< 0,001
Creatine (mg/dL)	0,8 ± 0,1	0,8 ± 0,2	0,9 ± 0,1	2,2 ± 1,4 ××× ↑↑↑ ††	< 0,001
LDL (mg/dL)	93,0 ± 12,6	118,2 ± 26,2 ×××	120,0 ± 30,6 ××	113,1± 21,5 ××	0,002
Creatine (mg/dL)	149,4 ± 24,5	216,7 ± 208,0	205,3 ± 148,1	202,4 ± 157,3	0,377
Urine microalbuminuria level (mg/L)	10,9 ± 7,1	19,9 ± 5,7 ×××	102,5 ± 64,5 ××× ↑↑↑	1166 ± 605,7 ××× ↑↑↑ †††	< 0,001

* Kruskal-Wallıs test p value. ** Chi-square test p value.
Compared with the control group;× p<0.05, ×× p<0.01, ××× p<0.001.
Compared with the normoalbuminuria group;↑ p<0.05, ↑↑ p<0.01, ↑↑↑ p<0.001.
Compared with the microalbuminuria group;† p<0.05, †† p<0.01, ††† p<0.001.
Fbg: Fasting blood glucose, Pbg: Postprandial blood glucose

Table 2: History of HT, obesity and drug use in the diabetic group

	Normoalbuminuria	Microalbuminuria	Overt albuminuria	p*
HT (n)	6	15	15	0,004
ACE inh & ARB usage (n)	2	13	10	0,001
Metformin usage (n)	17	10	2	< 0,001
Other OAD usage (n)	9	10	2	0,015
Insulin usage (n)	8	13	18	0,004
Mixed insulin usage (n)	6	13	12	0,209
BMI > 30 (kg/m2)(n)	7	7	3	0,269

* Chi-square test value.

Table 3 presents the blood and urine adropin levels and statistical comparisons between the healthy control and study groups. Serum adropin levels were observed to be elevated in the overt albuminuria group relative to the healthy control, normoalbuminuria, and microalbuminuria groups (p=0.007, p<0.001, p=0.008, respectively). Urinary adropin levels were observed to be elevated in the normoalbuminuria and overt albuminuria groups relative to the control group (p=0.002, p=0.001, respectively). Conversely, no statistically significant difference was noted in the microalbuminuria group. Urinary adropin levels were observed to be elevated in the normoalbuminuria and overt albuminuria groups relative to the microalbuminuria group (p=0.026 for both groups) (Figure 1).

Table 4 presents the blood and urine adropin levels and statistical comparisons between the healthy control and nephropathy groups. A comparison of the healthy control group with the nephropathy group revealed that adropin levels in the blood were higher in the former (p=0.013), while no difference was observed in urine adropin levels.

Following correlation tests conducted on diabetic patients, a positive correlation was identified between urinary microalbumin levels and serum adropin levels (p=0.002, r=0.400) (Table 5).

Table 3: Blood and urine adropin levels in the study groups

	Control (n=20)	Normoalbuminuria (n=20)	Microalbuminuria (n=20)	Overtly albumi-nuria (n=20)	P *
Serum adropine (ng/mL)	4,671±1,225 ×	4,065±1,144 ××	4,460±1,756 ×	6,272±2,873	0,002
Urine adropine (ng/mL)	9,444±4,102	16,627±7,672 † ↑	11,386±4,704	15,960±7,231 † ↑	0,001

* Kruskal-Wallıs test p value. Subgroups were compared with Mann whitney test.
Compared with the control group;† p<0.01, †† p<0.001.
Compared with the microalbuminuria group;↑ p<0.05
Compared with the overt albuminuria group;× p<0.01, ×× p<0.001.

Table 4: Serum and urine adropin levels according to the presence of nephropathy in the diabetic group

	Nephropathy (n=40)	None nephropathy (n=20)	p *
Serum adropine (ng/mL)	5,366 ± 2,518	4,065 ± 1,144	0,013
Urine adropine (ng/mL)	13,673 ± 6,451	16,627 ± 7,672	0,145

* Mann-Whitney test p value.

Table 5: Correlation of microalbumin with blood and urine adropin in diabetic group

		Serum adropine	Urine adropin
Microalbuminuria	r	0,400	0,050
	p*	0,002	0,704

* Pearson correlation test p value

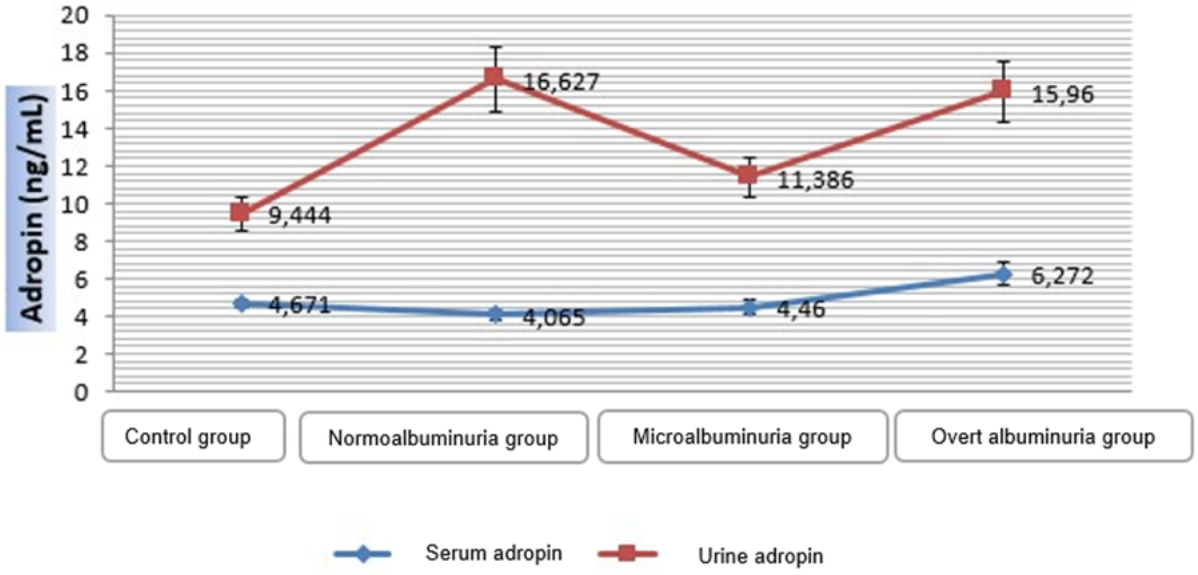

Figure 1: Blood and urine adropin levels in healthy control group and patient groups

[± SEM (Standard Eror of Meaning) value used]

3.2 Discussion

Serum adropin levels were found to be 4,671 ± 1,225 ng/mL in healthy controls, 4,065 ± 1,144 ng/mL in the normoalbuminuric group, 4,460 ± 1,756 ng/mL in the microalbuminuric group and 6,272 ± 2,873 ng/mL in the overt albuminuric group (p=0.002). The serum adropin level was found to be elevated in the group with overt albuminuria in comparison to the other study groups (p=0.007, p<0.001, p=0.008, respectively). Although not statistically significant, serum adropin levels were found to be decreased in the normoalbuminuric and microalbuminuric groups in comparison to the healthy controls. A positive correlation was observed between microalbuminuria and serum adropin levels in diabetic patients (p=0.002, r=0.400).

Diabetic nephropathy (DN) represents a significant complication of diabetes mellitus, characterized by progressive kidney damage and dysfunction (6). Recent studies have demonstrated the involvement of adropin, a peptide hormone, in the pathological mechanisms underlying diabetic nephropathy (10, 11). Adropin is recognized as a regulator of glucose and lipid metabolism. Alterations in adropin levels have been observed in a range of metabolic disorders, including diabetes and its associated complications (12). This analysis synthesizes the findings of several studies that have investigated the relationship between adropin levels and diabetic nephropathy (11, 13, 14).

A number of studies have indicated that serum adropin levels are considerably altered in individuals exhibiting diabetic nephropathy. For instance, Hu and Chen (2016) observed that adropin was expressed at a heightened level in the kidneys of rats with experimentally induced diabetes when compared to control groups (11). This finding suggests that there may be a compensatory mechanism in response to hyperglycemia and renal injury. This finding supports the conclusions of Berezina et al., who have noted that adropin has been investigated as a potentially useful biomarker for T2DM-induced nephropathy, indicating its potential role in the early detection and monitoring of diabetic kidney disease (15). Moreover, the study by Prystupa et al. corroborated these findings, demonstrating that increased adropin concentrations were observed in patients with diabetic nephropathy, thereby suggesting a protective role against renal damage (16).

Furthermore, the relationship between adropin levels and insulin resistance is of great relevance in the context of diabetic nephropathy. Taha's research

indicated that adropin has the effect of enhancing insulin sensitivity, which is a crucial factor in glucose metabolism and may serve to mitigate the progressive deterioration of diabetic complications, including nephropathy (17). Similarly, Li et al. (2021) have demonstrated that reduced serum levels of adropin are associated with enhanced insulin resistance, which in turn amplifies the likelihood of developing diabetic nephropathy (18). This inverse relationship between adropin levels and insulin resistance illustrates the potential of the peptide as a therapeutic target in the pharmacological management of diabetic nephropathy.

Furthermore, the anti-inflammatory effects of adropin have been consistently demonstrated in a multitude of scientific investigations. Ashour et al. (2019) have documented a reduction in the expression of pro-inflammatory cytokines following the administration of adropin, a factor that is often elevated in diabetic nephropathy (19). This anti-inflammatory effect may be a contributing factor to the renoprotective role of adropin, due to the fact that chronic inflammation is a key factor in the progression of diabetic kidney disease (20). Furthermore, the study by Kaur indicated the existence of a correlation between adropin levels and various biomarkers of renal function and cardiovascular health, supporting the hypothesis that adropin may play a multidimensional role in the pathophysiology of diabetic nephropathy (21).

The modulating effect of adropin on metabolic pathways further illustrates its importance in diabetic nephropathy. Azab et al. have demonstrated that adropin administration significantly reduces blood glucose and insulin levels in diabetic rats, which implies that adropin may help to restore metabolic balance in the context of diabetes(22). This metabolic regulation is crucial because hyperglycemia and insulin resistance are primary factors in diabetic nephropathy. Furthermore, findings by Guo et al. suggested that adropin may exert nephroprotective effects by modulating inflammatory responses and oxidative stress, which are crucial in the process of diabetic nephropathy (23).

In additional to its protective effects, the role of adropin as a potential biomarker for the early detection of diabetic nephropathy has been evaluated. The research by Rizk et al. demonstrated that serum adropin levels could serve as an early indicator of renal dysfunction in diabetic patients, providing a valuable tool for clinicians in the management of diabetes-related complications (24). This is particularly relevant given the increasing prevalence of diabetes and its associated complications worldwide.

The diversity of adropin's role in diabetic nephropathy is further emphasised by its interaction with various signalling pathways. Thapa et al. have identified a novel GPCR-MAPK-PDK4 pathway that adropin utilizes to regulate metabolic processes in cardiac cells, which indicates that related mechanisms may be involved in renal tissues (25). Understanding these pathways may lead the way to targeted therapies aimed at enhancing adropin signal transduction to relieve the effects of diabetic nephropathy.

Dietary factors also influence adropin levels. Studies have shown that carbohydrate consumption is inversely associated with plasma adropin concentrations, indicating that dietary macronutrient intake can significantly affect adropin levels (26, 27). This relationship highlights the importance of diet in managing metabolic health and suggests that dietary interventions could modulate adropin levels, thereby influencing metabolic outcomes.

The diversity in serum adropin levels across studies may be related to some populations in which adropin receptor resistance is predominant, similar to DM. The phenomenon of adropin receptor resistance is a critical area of investigation, particularly in the context of metabolic disorders such as obesity and diabetes. This resistance may contribute to the pathophysiology of these conditions by impairing the beneficial effects of adropin on glucose metabolism and endothelial function.

Research indicates that adropin exerts various physiological effects through its interaction with

specific receptors, notably the G protein-coupled receptor GPR19 Stelcer et al. (2020) (28). However, in states of obesity and insulin resistance, the efficacy of adropin may be diminished, leading to what can be termed "adropin receptor resistance." This resistance could be attributed to several mechanisms, including receptor downregulation, desensitization, or alterations in downstream signaling pathways.

For instance, studies have shown that in obese individuals, serum adropin levels are often elevated, yet this does not correlate with improved metabolic outcomes (29, 30). This paradox suggests that while adropin is present, its action may be hindered, potentially due to receptor desensitization or the presence of inflammatory cytokines that interfere with its signaling pathways. Inflammatory states are known to impair insulin signaling and may similarly affect adropin receptor functionality, leading to a diminished response to the peptide (31, 32)

Moreover, the role of adropin in vascular health is well-documented, as it has been shown to enhance nitric oxide production and improve endothelial function (7, 33). However, in conditions such as chronic kidney disease and diabetes, the protective effects of adropin may be blunted due to receptor resistance. For example, in diabetic nephropathy, the expression of adropin and its receptor may be altered, contributing to vascular dysfunction and exacerbating renal damage (34). This highlights the importance of understanding the mechanisms underlying adropin receptor resistance, as it may provide insights into therapeutic strategies aimed at restoring the peptide's beneficial effects.

Additionally, the interplay between adropin and other metabolic hormones, such as insulin and leptin, further complicates the landscape of receptor resistance. In insulin-resistant states, the synergistic effects of these hormones may be disrupted, leading to a compounded effect on adropin signaling (29, 30). This interaction underscores the necessity of a holistic approach in addressing metabolic disorders, where restoring adropin sensitivity could be a pivotal component of treatment strategies.

Urinary adropin levels were found to be 9.444 ± 4.102 ng/mL in healthy controls, 16.627 ± 7.672 ng/mL in the normoalbuminuric group, 11.386 ± 4.704 ng/mL in the microalbuminuric group, and 15.960 ± 7.231 ng/mL in the overt albuminuric group ($p = 0.001$). A comparison of urinary adropin levels between the healthy control group and the normoalbuminuric and overt albuminuric groups revealed a statistically significant difference ($p=0.002$ and $p=0.001$, respectively). Similarly, a comparison between the microalbuminuric group and the normoalbuminuric and overt albuminuric groups demonstrated a statistically significant difference in urinary adropin levels ($p=0.026$ for both). Furthermore, the urinary adropin level was determined to be 14.658 ± 6.960 ng/mL in all diabetic patients without nephropathy discrimination, which was found to be significantly higher than that observed in healthy controls ($p=0.001$).

The increase in urinary adropin levels has garnered attention in recent research due to its implications in metabolic regulation and potential associations with various health conditions. Notably, studies have shown that urinary adropin concentrations can be significantly higher than serum levels, with normal urinary adropin concentrations being approximately four times higher than corresponding serum levels (35).

The relationship between adropin levels and metabolic disorders is complex. For example, in patients with type 2 diabetes mellitus (T2DM), serum adropin levels are often found to be lower and inversely correlated with adverse metabolic parameters such as fasting glucose and HbA1c levels (36). This suggests that while urinary adropin levels may increase in response to certain metabolic stresses or conditions, serum levels may decrease, indicating a potential compensatory mechanism or response to metabolic dysregulation (12, 37)

In addition, the role of Adropin in renal function has been highlighted, particularly in chronic kidney disease (CKD). Research suggests that adropin treatment may ameliorate renal damage by

modulating inflammatory responses and matrix metalloproteinases, which are critical in renal pathology (32, 38). This suggests that increased levels of adropin in urine may be a response to renal stress or injury, and may serve as a biomarker of renal function and metabolic health (11).

4. CONCLUSION

In conclusion, the data indicate that adropin levels are markedly altered in diabetic nephropathy, suggesting its potential utility as both a biomarker and a therapeutic target in this condition. Given its involvement in the modulation of insulin sensitivity, inflammation, and various metabolic pathways, the peptide plays an integral role in the pathophysiology of diabetic kidney disease. The observed increase in urinary adropin levels reflects a complex interplay between metabolic health, renal function, and dietary influences. Consequently, future research should aim to elucidate the mechanisms through which adropin influences renal function and to investigate its therapeutic potential in metabolic disorders, particularly in the context of diabetic nephropathy. Furthermore, the emerging concept of adropin resistance highlights the necessity for continued exploration of its implications in the pathogenesis and treatment of diabetic kidney disease.

Acknowledgements: I would like to express my gratitude to all my professors who provided invaluable assistance in the preparation of my thesis, as well as to the Fırat University Endocrinology Clinic.

Financial Support: This research received no grant from any funding agency/sector.

Conflicts of Interest: The authors declared that there is no conflict of interest.

Ethical Statement: This study was approved by the Fırat University Faculty of Medicine Clinical Studies Ethics Committee (97521439-110/13-02-03).

REFERENCES

1. Ceriello A., Prattichizzo F., Variability of risk factors and diabetes complications, Cardiovascular diabetology 20(1), (2021), 101.
2. Abdul Basith Khan M., Hashim M.J., King J.K., Govender R.D., Mustafa H., Al Kaabi J., Epidemiology of type 2 diabetes–global burden of disease and forecasted trends, Journal of epidemiology and global health 10(1), (2020), 107-111.
3. Samsu N., Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment, BioMed research international 2021(1), (2021), 1497449.
4. Qi C., Mao X., Zhang Z., Wu H., Classification and differential diagnosis of diabetic nephropathy, Journal of diabetes research 2017(1), (2017), 8637138.
5. Thipsawat S., Early detection of diabetic nephropathy in patient with type 2 diabetes mellitus: A review of the literature, Diabetes and Vascular Disease Research 18(6), (2021), 14791641211058856.
6. Elendu C., Okah M.J., Fiemotongha K.D., Adeyemo B.I., Bassey B.N., Omeludike E.K., Obidigbo B., Comprehensive advancements in the prevention and treatment of diabetic nephropathy: A narrative review, Medicine 102(40), (2023), e35397.
7. Ali I.I., D'Souza C., Singh J., Adeghate E., Adropin's role in energy homeostasis and metabolic disorders, International journal of molecular sciences 23(15), (2022), 8318.
8. Jasaszwili M., Billert M., Strowski M.Z., Nowak K.W., Skrzypski M., Adropin as a fat-burning hormone with multiple functions—Review of a decade of research, Molecules 25(3), (2020), 549.
9. Gunraj R.E., Yang C., Liu L., Larochelle J., Candelario-Jalil E., Protective roles of adropin in neurological disease, American Journal of Physiology-Cell Physiology 324(3), (2023), C674-C678.
10. Es-Haghi A., Al-Abyadh T., Mehrad-Majd H., The clinical value of serum adropin level in early detection of diabetic nephropathy, Kidney and Blood Pressure Research 46(6), (2021), 734-740.
11. Hu W., Chen L., Association of serum adropin concentrations with diabetic nephropathy, Mediators of inflammation 2016(1), (2016), 6038261.
12. Soltani S., Beigrezaei S., Malekahmadi M., Clark C.C., Abdollahi S., Circulating levels of adropin and diabetes: a systematic review and meta-analysis of observational studies, BMC Endocrine Disorders 23(1), (2023), 73.
13. Yu M., Wang D., Zhong D., Xie W., Luo J., Adropin carried by reactive oxygen species-responsive nanocapsules ameliorates renal lipid toxicity in diabetic mice, ACS Applied Materials & Interfaces 14(33), (2022), 37330-37344.
14. Li B., Tian X., Guo S., Zhang M., Li J., Zhai N., Wang H., Zhang Y., Pentraxin-3 and adropin as inflammatory markers of early renal damage in type 2 diabetes patients, International urology and nephrology 52(11), (2020), 2145-2152.
15. Berezina T.A., Obradovic Z., Boxhammer E., Berezin A.A., Lichtenauer M., Berezin A.E., Adropin predicts chronic kidney disease in type 2 diabetes mellitus patients with chronic heart failure, Journal of Clinical Medicine 12(6), (2023), 2231.
16. Prystupa A., Kiciński P., Luchowska-Kocot D., Sak J., Prystupa T., Chen K.-H., Chen Y.-H., Panasiuk L., Załuska W., Afamin and adropin in patients with alcohol-induced liver cirrhosis, Annals of Agricultural and Environmental Medicine 25(3), (2018), 527-531.
17. Taha M.M., Muhsen S.N., Evaluation of Adropin Levels in

Cardiovascular Disease, Journal of Prevention, Diagnosis and Management of Human Diseases 4(01), (2024), 22-30. https://doi.org/10.55529/jpdmhd.41.22.30

18. Li N., Xie G., Zhou B., Qu A., Meng H., Liu J., Wang G., Serum adropin as a potential biomarker for predicting the development of type 2 diabetes mellitus in individuals with metabolic dysfunction-associated fatty liver disease, Frontiers in physiology 12 (2021), 696163.
19. Ashour W.M., Abdel-Aleem D., Khalil S.S., Elkazzaz O.M., Serum adropin and vaspin levels in obese rats with polycystic ovary syndrome and after metformin treatment, Zagazig University Medical Journal 27(2), (2021), 193-202.
20. Rayego-Mateos S., Rodrigues-Diez R.R., Fernandez-Fernandez B., Mora-Fernández C., Marchant V., Donate-Correa J., Navarro-González J.F., Ortiz A., Ruiz-Ortega M., Targeting inflammation to treat diabetic kidney disease: the road to 2030, Kidney international 103(2), (2023), 282-296.
21. Kaur R., Krishan P., Kumari P., Singh T., Singh V., Singh R., Ahmad S.F., Clinical Significance of Adropin and Afamin in Evaluating Renal Function and Cardiovascular Health in the Presence of CKD-MBD Biomarkers in Chronic Kidney Disease, Diagnostics 13(19), (2023), 3158.
22. Azab M.M.A., Mady N.M., El Bendary E.M., El Sawy S.A., A Cross Talk Between Adropin and Possible Metabolic Syndrome Disorders in Experimental Male Albino Rats, International journal of health sciences 6(S4), 9815-9834.
23. Guo L., Jiang B., Li D., Xiao X., Nephroprotective effect of adropinin against streptozotocin-induced diabetic nephropathy in rats: inflammatory mechanism and YAP/TAZ factor, Drug Design, Development and Therapy (2021), 589-600.
24. Rizk F.H., El-Saka M.H., Ibrahim R.R., El-Deeb O.S., Ibrahim H.A., El Saadany A.A., Mashal S.S., Ammar L., Abdelsattar A.M., Barhoma R.A., Possible mitigating effect of adropin on lung injury in diabetic rats: Targeting the role of Rho A/Rho-associated kinase pathway, BioFactors 49(4), (2023), 928-939.
25. Thapa D., Stoner M.W., Zhang M., Xie B., Manning J.R., Guimaraes D., Shiva S., Jurczak M.J., Scott I., Adropin regulates pyruvate dehydrogenase in cardiac cells via a novel GPCR-MAPK-PDK4 signaling pathway, Redox biology 18 (2018), 25-32.
26. Stevens J.R., Kearney M.L., St-Onge M.P., Stanhope K.L., Havel P.J., Kanaley J.A., Thyfault J.P., Weiss E.P., Butler A.A., Inverse association between carbohydrate consumption and plasma adropin concentrations in humans, Obesity 24(8), (2016), 1731-1740.
27. Butler A.A., St-Onge M.-P., Siebert E.A., Medici V., Stanhope K.L., Havel P.J., Differential responses of plasma adropin concentrations to dietary glucose or fructose consumption in humans, Scientific reports 5(1), (2015), 14691.
28. Stelcer E., Milecka P., Komarowska H., Jopek K., Tyczewska M., Szyszka M., Lesniczak M., Suchorska W., Bekova K., Szczepaniak B., Adropin stimulates proliferation and inhibits adrenocortical steroidogenesis in the human adrenal carcinoma (HAC15) cell line, Frontiers in endocrinology 11 (2020), 561370.
29. Ganesh-Kumar K., Zhang J., Gao S., Rossi J., McGuinness O.P., Halem H.H., Culler M.D., Mynatt R.L., Butler A.A., Adropin Deficiency Is Associated With Increased Adiposity and Insulin Resistance, Obesity 20(7), (2012), 1394-1402. https://doi.org/10.1038/oby.2012.31
30. Gao S., McMillan R.P., Zhu Q., Lopaschuk G.D., Hulver M.W., Butler A.A., Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance, Molecular metabolism 4(4), (2015), 310-324.
31. Zhang S., Chen Q., Lin X., Chen M., Liu Q., A review of adropin as the medium of dialogue between energy regulation and immune regulation, Oxidative medicine and cellular longevity 2020(1), (2020), 3947806.
32. Yazgan B., Avcı F., Memi G., Tastekin E., Inflammatory response and matrix metalloproteinases in chronic kidney failure: Modulation by adropin and spexin, Experimental Biology and Medicine 246(17), (2021), 1917-1927.
33. Lovren F., Pan Y., Quan A., Singh K.K., Shukla P.C., Gupta M., Al-Omran M., Teoh H., Verma S., Adropin is a novel regulator of endothelial function, Circulation 122(11_suppl_1), (2010), S185-S192.
34. Ibrahim M.E., El-Din D.N., Alkot A.M., Mansour A.E., Amer H.G., Assessment of serum adropin level in type 2 diabetic patients with or without nephropathy, Journal of The Arab Society for Medical Research 16(1), (2021), 17-23.
35. Gu X., Li H., Zhu X., Gu H., Chen J., Wang L., Harding P., Xu W., Inverse correlation between plasma adropin and ET-1 levels in essential hypertension: A cross-sectional study, Medicine 94 (40), (2015), e1712.
36. Chachan T.A.K.A., Farhna H., Hamed S., Jawad A.A., Determination of adropin, body mass index and other biochemical parameters in Iraqi type II diabetic patients, International Journal of Health Sciences (V), (2022), 431322.
37. Alzoughool F., Al Hourani H., Atoum M., Bateineh S., Abu shaikh H., Al-Zghool H., Al-Shudifat A.-e., Evaluation of serum adropin and irisin levels and its association with anthropometric obesity indices and biochemical parameters in Type 2 diabetic patients, Nutrition and Healthy Aging 6(3), (2021), 191-198.
38. Memi G., Yazgan B., Adropin and spexin hormones regulate the systemic inflammation in adenine-induced chronic kidney failure in rat, Journal of Physiology Investigation 64(4), (2021), 194-201.