Section: Biochemistry

Original Research Article

EVALUATION OF SERUM ADROPIN AS A BIOMARKER IN DIFFERENT STAGES OF DIABETIC NEPHROPATHY: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Adropin, a 76-amino acid peptide hormone secreted from neuronal tissues and liver cells, has emerged as a potential biomarker in metabolic disorders. Derived from the energy homeostasis-associated ENHO protein, adropin demonstrates involvement in glucose metabolism regulation. This investigation examined serum adropin levels as a predictive biomarker for diabetic nephropathy progression among Type 2 Diabetes Mellitus (T2DM) patients across different albuminuria stages. **Materials and Methods:** This cross-sectional study conducted at a South Indian tertiary care facility (June 2021–May 2022) enrolled 120 T2DM patients and 60 healthy controls. Participants were stratified into three groups (n=40 each) based on urinary albumin-creatinine ratio (UACR): normoalbuminuria (<30 mg/g), microalbuminuria (30–300 mg/g), and macroalbuminuria (>300 mg/g). Serum adropin concentrations were quantified using enzyme-linked immunosorbent assay (ELISA). Statistical analysis employed ANOVA, correlation analysis, and independent T-test. **Result:** Mean serum adropin levels were significantly higher in controls (5.1±0.4 ng/ml) compared to normoalbuminuria (3.4±0.25 ng/ml), microalbuminuria (2.5±0.14 ng/ml), and macroalbuminuria (1.7±0.39 ng/ml) groups (p=0.0001). Strong positive correlation existed between adropin and estimated glomerular filtration rate (eGFR) (r=0.674, p=0.0001). Significant negative correlations were observed with albumin creatinine ratio (r=-0.833, p=0.0001), serum creatinine (r=-0.689, p=0.0001), urine albumin (r=-0.840, p=0.0001), blood urea nitrogen (r=-0.616, p=0.0001), and blood pressure parameters (p=0.0001). **Conclusion:** Serum adropin levels demonstrate progressive decline with advancing diabetic nephropathy severity, showing strong positive correlation with eGFR and negative correlations with traditional renal parameters. These findings suggest serum adropin may serve as a novel biomarker for diabetic nephropathy assessment and staging.

INTRODUCTION

The endocrine disorder known as diabetes mellitus contributes to chronic disease burden globally. Elevated blood sugar levels cause end-organ damage in kidney, brain, heart, liver, and eyes. Approximately 465 million patients worldwide have type 2 diabetes mellitus.[1] The International Diabetes Federation reports approximately four million annual diabetes-related deaths, with 81% occurring in middle- and low-income nations.[2] India has approximately 80 million patients with type 2 diabetes mellitus, with projections indicating doubling of cases among individuals aged >65 years by 2050.[3] Tamil Nadu demonstrates the highest diabetes prevalence in India.[4]

Diabetic nephropathy represents a major complication, constituting the primary cause of chronic kidney disease (41% globally) and contributing to 75% of myocardial infarctions related to thrombosis.[5,6] The increasing trend of diabetic nephropathy in India is noteworthy.[7] End-stage renal disease develops when eGFR falls below 15 ml/min/1.73m².[8] Diagnosis depends on pathological albuminuria presence,[9] requiring routine albumin monitoring.[10] However, nephropathy may exist

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without albuminuria, creating diagnostic challenges when clinically significant damage remains undetected,[11] necessitating novel biomarkers for early diagnosis.[12]

Adropin, a 76-amino acid hormone primarily secreted from neuronal and hepatic tissues, emerges from the energy homeostasis-associated ENHO protein.[13] Studies demonstrate adropin's role in glucose metabolism, showing reduced insulin resistance and enhanced glucose utilization in adropin-treated obese mice.[14] Serum adropin levels are reduced in uncontrolled hyperglycemia.[15] Adropin demonstrates vascular endothelial protective properties through nitric oxide maintenance,[16,17] with evidence suggesting prevention of macrovascular complications.[18] This investigation examined serum adropin associations with diabetic nephropathy in T2DM patients compared to healthy controls.

MATERIALS AND METHODS

Study design, period, and participants

The cross-sectional investigation had been carried out in a South Indian tertiary care facility. Throughout the course of the one-year trial period (June 2021–May 2022), data from patients having T2DM, along with healthy individuals, were gathered from the outpatient clinic of the Department of General Medicine and Nephrology.

Inclusion Criteria

Participants, of age more than 18 years, who gave their consent to take part were also included in this research.

Exclusion Criteria

The recent occurrence of infective diseases, subjects with other immunological disorders, presence of other cardiac abnormalities, raised blood pressure levels, cancer, and the presence of other endocrine diseases were the criteria used for excluding participants.

Sample size and sampling method

The size of the sample had been computed using a prior study on the association between nephropathy along with type 2 diabetes mellitus.[19] Assuming an alpha error of 0.05 (two-tailed) and power of 90 percent, the size of the sample had been calculated. All patients attending the outpatient clinic in the Department of General Medicine and Nephrology in Thanjavur Medical College had been selected consecutively between June 2021 and May 2022.

Selection of Participants

The standard diagnostic guidelines by ADA for diabetes diagnosis were used (fasting plasma glucose ≥126 mg/dl, postprandial ≥200 mg/dl, HbA1c >6.5% with or without complications).[20] Diabetic nephropathy is said to be present if there is an increase in the urinary albumin-creatinine ratio (UACR >30 mg/g) and decreased renal function, with eGFR below 90 ml/min/1.73m².[21]

Based on the urine albumin to creatinine ratio, or ACR, 120 T2DM individuals were split into 3 groups: the normoalbuminuric group (ACR <30 mg/g; n=40), the microalbuminuria group (30 ≤ACR ≤300 mg/g; n=40), and the macroalbuminuria group (ACR >300 mg/g; n=40).[22] Totally, sixty people were selected as controls (people who have normoglycemia and are not under any form of treatment).

Ethical approval and informed consent: All participants gave informed consent before being included in the study. The protocol was approved by the institutional ethical committee of Thanjavur Medical College Hospital with an approval number of 687/2020.

Data collection procedure: A thorough history was taken, followed by a full body general examination. The age of the patient, the chronology of the development of the disease, gender, blood pressure levels, and other anthropometric data were recorded.

Sample collection: The sample was collected following the standard operating protocol. The patient was asked to follow the NPO (nil per oral) for 12 hours overnight. Then 6 ml of venous blood was collected. The second sample had been collected 2 hours after morning food intake. After 30 minutes of clotting at room temperature, the sample was centrifuged for 20 minutes. The fluid in the supernatant layer was stored at a freezing temperature (below 20 degrees Celsius). Similarly, the urine samples were also centrifuged, and the fluid in the supernatant layer was stored at the same freezing temperature. Centrifugation was again carried out if there was the presence of urinary sediments.

Biochemical Measurements: The ELISA kit was used to measure the serum adropin levels. We used the standard glucose oxidase/peroxidase procedure to calculate fasting and postprandial blood glucose levels. We calculated urinary albumin using the Latex Agglutination Method. Modified Jaffe's method was used to assess serum creatinine concentration. Blood urea had been estimated by the Urease Glutamate Dehydrogenase (GLDH) Method and converted into BUN. The Cock Croft-Gault Equation had been applied to compute the estimated glomerular filtration rate (eGFR) after the serum creatinine had been determined by applying the modified Jaffe's technique.[23]

Statistical Analysis: Excel (Microsoft® Corp., Redmond, WA) was used to enter all the data, and IBM SPSS Statistical software version 26.0 (IBM Corp., 2019) was used for analysis. In demographic data, continuous variables have been stated as mean and standard deviation, as well as categorical variables are indicated by frequency as well as percentage. Ordinal binomial variables had been analyzed using the chi-square test. A one-way ANOVA had been utilized to measure the significance of the association between multiple groups and other continuous parameters. The Bonferroni post hoc test was used to add additional validity to the analysis. The linear link between

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Adropin and other factors was assessed using Spearman's correlation coefficient (r). The difference in Adropin mean values between genders was calculated applying the independent T-test. If a p-value was <0.05, it had been considered as significant.

RESULTS

[Table 1] presents baseline characteristics. Mean age significantly differed across groups (p=0.0001). Gender distribution showed variations (p=0.001). Progressive deterioration was observed in blood pressure, glycaemic parameters, and renal function markers across nephropathy stages (all p=0.0001). Most notably, serum adropin levels demonstrated progressive decline from controls (5.1±0.4 ng/ml) through normoalbuminuria (3.4±0.25 ng/ml), microalbuminuria (2.5±0.14 ng/ml), to macroalbuminuria (1.7±0.39 ng/ml) (p=0.0001).

Table 1: Demographic and clinical data of controls and different stages of albuminuria in T2DM patients.

Variables	Control (n=60)	Normo Albuminuria (n=40)	Micro Albuminuria (=40)	Macro Albuminuria (n = 40)	P value
Age (years)	36.6± 8.4	53.2 ± 8.2	53.9 ± 11.2	59.4 ± 12.3	0.0001
Gender (Male/ Female)	19/ 41	22/ 18	14/ 26	28/ 12	0.001*
Body Mass Index (Kg/m2)	24.6±2.9	25.6 ±2.4	25.5±2.9	25.3 ± 2.1	0.270
Systolic Blood Pressure (mm hg)	109 ± 6.2	125.4 ± 5.6	130.6 ± 4.3	137 ± 5.6	0.0001
Diastolic Blood Pressure (mm Hg)	71.3 ± 3.4	82.2 ± 4.7	85.1 ± 4.4	89.0 ± 3.0	0.0001
Fasting Blood Sugar (mg/dl)	73.40 ± 7.4	103.05 ± 35.4	89 ± 22.9	122.1 ± 55.3	0.0001
Postprandial Blood Sugar (mg/dl)	116.8 ± 7.2	184.4 ± 64.2	169.3 ± 47.5	193.2 ± 69.1	0.0001
Estimated Glomerular Filtration Rate (ml/ min)	111.5 ± 22.8	84.7 ± 16.5	71.8 ± 30.8	58.4 ± 24.0	0.0001
Serum Creatinine (mg/dl)	0.728 ± 0.08	0.855 ± 0.08	1.1 ± 0.4	1.4 ± 0.8	0.0001
Blood Urea Nitrogen (mmol/L)	3.4 ± 0.48	4.05 ± 0.85	4.2 ± 0.71	7.3 ± 5.6	0.0001
Adropin (ng/ml)	5.1 ± 0.4	3.4 ± 0.25	2.5 ± 0.14	1.7 ± 0.39	0.0001
Urine Albumin (mg/g)	0.31 ± 0.16	1.41 ± 3.21	5.4 ± 3.51	49.95 ± 44.39	0.0001
Urine Creatinine (mg/dl)	28.92 ± 2.63	42.15 ± 20.33	36.97 ± 21.43	69.46 ± 134.89	0.023
Albumin Creatinine Ratio (mg/g)	11.2 ± 6.5	14.0 ± 9.8	152.4 ± 66.7	1309.2 ± 1180	0.0001

*Chi-square test was used

Table 2: Correlation of various parameters with respect to Adropin levels in the study.

Variables	Mean	Std. Deviation	r	p value
Adropin	3.4608	1.3846	-	-
Age (years)	49.21	13.564	-0.639	0.0001
Gender* – Male Female	3.123 3.749	1.29 1.40	-	0.002
Body Mass Index (Kg/m2)	25.218	2.69412	-0.199	0.0001
Systolic Blood Pressure (mm Hg)	123.67	12.416	-0.847	0.0001
Diastolic Blood Pressure (mm Hg)	80.73	8.047	-0.808	0.0001
Fasting Blood Sugar (mg/dl)	94.28	37.632	-0.494	0.0001
Postprandial Blood Sugar (mg/dl)	160.49	58.497	-0.549	0.0001
Blood Urea Nitrogen (mmol/L)	4.619	3.0883	-0.616	0.0001
Serum Creatinine (mg/dl)	0.994	0.5337	-0.689	0.0001
Estimated Glomerular Filtration Rate (ml/ min)	84.96	31.569	0.674	0.0001
Urine Albumin (mg/g)	12.72038	28.919152	-0.840	0.0001
Urine Creatinine (mg/dl)	42.66243	66.245035	-0.049	0.003
Albumin Creatinine Ratio (mg/g)	331.7039	762.97232	-0.833	0.0001

*Independent T-test was used.

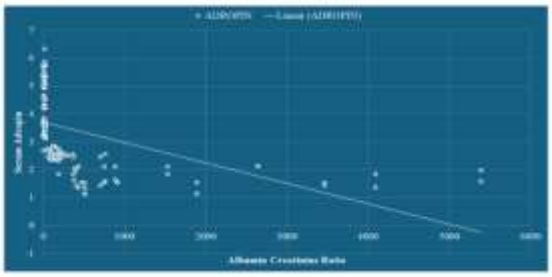

Figure 1: Scatter plot showing the association between serum Adropin levels and albumin creatinine ratio.

[Table 2] presents correlation analysis between serum adropin and various clinical parameters. Overall mean adropin level was 3.4608±1.3846 ng/ml. Strongest positive correlation existed with eGFR (r=0.674, p=0.0001). Significant negative correlations were observed with albumin creatinine ratio (r=-0.833, p=0.0001), urine albumin (r=-0.840, p=0.0001), systolic blood pressure (r=-0.847, p=0.0001), diastolic blood pressure (r=-0.808, p=0.0001), serum creatinine (r=-0.689, p=0.0001), blood urea nitrogen (r=-0.616, p=0.0001), and age (r=-0.639, p=0.0001). Gender analysis showed male

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(3.123±1.29 ng/ml) versus female (3.749±1.40 ng/ml) with p=0.002.

[Figure 1] illustrates scatter plot showing strong negative correlation between serum adropin levels and albumin creatinine ratio (r=-0.833, p=0.0001). [Figure 2] demonstrates scatter plot depicting significant negative correlation between serum adropin levels and serum creatinine (r=-0.689, p=0.0001). These graphical representations validate the tabulated correlation findings and visually demonstrate the inverse relationships between adropin and key nephropathy markers.

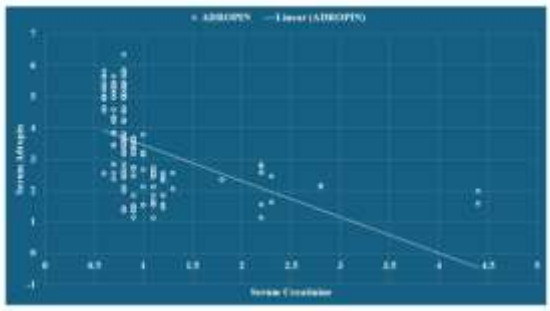

Figure 2: Scatter plot showing the association between serum Adropin levels and serum creatinine.

DISCUSSION

Renal function tends to undergo irreversible damage because of various factors, such as infection, autoimmune diseases, inflammation, and diabetes. The chief cause among all these is diabetes mellitus type 2. Untreated or poorly managed blood sugar levels in these patients lead to micro and macro complications like retinopathy, neuropathy, and nephropathy. Even among patients who have adequate control of blood sugar levels, there is an increasing trend of end-stage renal disease. Hence, it is imperative to identify biomarkers to catch the disease early and to nip the bud of renal organ damage early in its pathogenesis. Many biomarkers are currently under study to identify early pathogenesis. Clinicians use urine albumin excretion to determine the severity of renal parenchymal damage. Albuminuria is predominantly used to detect the onset and severity of diabetic nephropathy, even though it lacks both sensitivity and specificity. It is imperative to note that some diabetic nephropathy patients with significant parenchymal damage do not present with albuminuria. According to certain studies, renal tubular damage starts even before the appearance of micro-albumin in urine. Finding markers that can identify nephropathy in its early stages is crucial. Kidney biopsies can be one option for patients. But this is not useful in therapeutic contexts.

With advances in the study of biomarkers, it is increasingly becoming possible to identify renal tubular injury early in diabetic renal disease. The normal adropin levels in serum tend to decline with renal tubular damage. Earlier studies have demonstrated that the higher the tubular damage, the greater is the decline in the level of serum adropin. In this investigation, we tried to study further the extent of the drop in levels of serum Adropin according to the extent of renal tubular damage.

Our results showed a statistical association between the groups who had significant renal damage compared to the patients without renal damage. Further, in our study, when there is more metabolism-related damage among the patients, it corresponds with a significant reduction in serum adropin levels. These findings raise the possibility of adropin-mediated protection against metabolic disorders and diabetic nephropathy among diabetic patients.

In this animal study, Adropin's potential function in raising the insulin sensitivity as well as increasing the metabolism of glucose was studied among lab mice.[19] The mouse population was artificially made diabetic by injection of streptozotocin. After making the mice diabetic, the effect of serum adropin in reducing the artificially induced diabetes state was studied. The results showed an enhanced glucose homeostatic mechanism coupled with increased insulin sensitivity. The state of insulin resistance is reduced.[14] Further, when the adropin was removed from the mice, they exhibited a characteristic dyslipidemic state with increased fat mass and increased body weight. Many other studies were done, replacing animal-based with human-based studies to study the possible correlation between adropin and metabolic complications of diabetes.

Interestingly, some studies have found an important linkage between the levels of serum adropin and the advancement of gestational diabetes among pregnant women. As before, the level of serum adropin was found to be lower among gestational diabetes patients.[25]

A similar reduction in serum Adropin concentrations was found in an investigation conducted by Zang et al., especially in overweight/obese subjects. Another study by Wu et al. reported a remarkable reduction in the level of serum Adropin along with a close association between cholesterol-laden atherosclerotic plaques in patients with type 2 diabetes mellitus.[24]

Our results were consistent with the findings in many other studies on the correlation between serum adropin levels and diabetic nephropathy. Our investigation revealed a steady decline in serum adropin levels linked with the development of diabetic nephropathy in individuals having type 2 diabetes. Our study results could add to the existing literature supporting the use of serum adropin as a reliable biomarker for the prediction of diabetic nephropathy in the future.

Limitation: First, it is unclear whether nephropathy has developed as a result of Adropin decrease or vice versa due to the study's cross-sectional methodology. Therefore, more long-term research is required to clarify the causal relationship. Secondly, the measurements of Adropin concentrations were limited to fasting settings, which may not accurately represent Adropin variations over time, particularly following dietary modifications. Adropin's reaction

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to altered metabolic status may be explained by taking into account the kinetics of its clearance from the circulation and evaluating its concentration in different situations.

CONCLUSION

According to the current study's findings, diabetic patients with nephropathy had considerably lowered serum Adropin levels to healthy, non-diabetic subjects. A substantial positive connection was seen between the levels of serum Adropin and eGFR. With the exception of eGFR, a significant negative correlation had been observed between Adropin levels and all other variables, including BUN, urine creatinine, urine albumin, serum creatinine, albumin creatinine ratio, systolic and diastolic blood pressure, fasting, and postprandial blood sugar levels. For this reason, serum Adropin may be used as a biomarker to estimate the likelihood of developing diabetic nephropathy. To confirm our findings, especially at the molecular levels, multi-centered research with larger sample size is necessary.

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