E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2024; 6(3): 36-43
www.medicinepaper.net
Received: 24-05-2024
Accepted: 30-06-2024

Ahmed Alsayed Huntsh
Resident Physician, Department of Nephrology, Ahmed Maher Teaching Hospital, Egypt

Shireen Ali Elhoseny
Assistant Professor, Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

Rasha Adel Elkholy
Lecturer, Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Tamer AbdElhamid Elbedewy
Professor, Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Corresponding Author:
Ahmed Alsayed Huntsh
Resident Physician, Department of Nephrology, Ahmed Maher Teaching Hospital, Egypt

Serum adropin as a biomarker of diabetic nephropathy in type 2 diabetic patients

Ahmed Alsayed Huntsh, Shireen Ali Elhoseny, Rasha Adel Elkholy and Tamer AbdElhamid Elbedewy

DOI: https://doi.org/10.22271/27069567.2024.v6.i3a.568

Abstract
Background: Adropin (AD) regulates the metabolic balance of the heart, blood vessels, kidneys, along with skeletal muscles in relation to nutritional condition. Our research was designed to assess if serum AD levels could be implemented as a biomarker for diabetic nephropathy among cases developing T2DM.
Methods: The case-control study included 60 adult patients above 18 years old of both sexes who develop T2DM in addition to 20 subjects in good health as a control group. Our team categorized all subjects equally into four groups. Group (1): involved twenty nondiabetic controls. Group (2) involved twenty adult cases developing T2DM and normal albuminuria [urinary albumin creatinine ratio (UACR) below 30 mg\gm)]. Group (3) included 20 adult cases developing T2DM and microalbuminuria (UACR below 30 mg\gm). Group (4) included 20 adult cases developing T2DM and macroalbuminuria (UACR over 300 mg\gm).
Results: AD can significantly predict diabetic nephropathy (AUC = 0.907) at cut-off 225 with 90% sensitivity, and 85% specificity. A significant negative association was noted among serum AD as well as age, duration of disease, FBG, 2HPPG, glycated hemoglobin, UACR, cholesterol, triglycerides, low-density lipoprotein, creatinine, blood urea nitrogen, uric acid. A significant positive relationship was also noted among AD and high-density lipoprotein, albumin, and hemoglobin. No association was found between AD and aspartate aminotransferase, alanine transaminase, total leucocyte count, platelets.
Conclusion: Serum AD level was significantly reduced among cases developing T2DM with microalbuminuria. Serum AD may promise alternative serum marker in terms of predicting DKD cases from diabetics.

Keywords: Adropin, diabetic nephropathy, predictor

Introduction
Diabetes mellitus (DM), frequently referred to as 'diabetes', stands as a metabolic condition which significantly impacts the body's glycemic control or its ability to manage blood glucose levels. DM is often characterized by intricate pathological processes along with potentially dangerous consequences. It is linked to many severe problems [1]. Diabetic nephropathy, commonly referred to as renal dysfunction, is a significant complication of the disease, which indicates a glomerular filtration rate reduction along with an elevation in albuminuria [2]. Approximately 30 to 35 percent of cases developing either type 1 or type 2 DM may exhibit diabetic nephropathy. New research highlights the significance of cytokines along with pro-inflammatory factors in the diabetic nephropathy progression [3].
Adropin (AD) is one of the peptides, which are identified and secreted in the brain as well as hepatic tissues, but further research has verified its presence in the kidneys, pancreas, heart, in addition to muscles. According to research, AD regulates glucose and lipid metabolism, which contributes to energy balance. It also has a broad variety of other functions [4]. Recent investigations have shown that AD may have an immunomodulatory function and have connected it to chronic inflammatory conditions. Serum levels of AD are much reduced in inflammatory bowel disease patients. Endothelial dysfunction may be the primary cause of the decrease in serum AD levels in several diseases, but the exact relationship is yet unclear [5].
Studies, addressing the correlation between AD and diabetic nephropathy, remain scarce.

This work was designed to assess serum AD level as a possible biomarker for DN among cases developing T2DM.

Subjects and Methods

We designed a case-control study that involves 60 adult patients (Above 18 years old) of both sexes who develop T2DM along with 20 subjects in good overall health as a control group.

We commenced our research after it got approved from the Ethical Committee Tanta University Hospitals (approval code: --). Our team asked all participants to sign a written consent.

Our team excluded cases developing T1DM, obesity with body mass index (BMI) over 30 kg\m^2, end stage kidney disorder, acute or chronic liver disease, renal impairment due to any other disease, pregnancy, and current or recent urinary tract infection.

All participants were equally categorized into the following groups.

- **Group (1):** 20 healthy normal nondiabetic controls
- **Group (2):** 20 adult cases developing T2DM and normal albuminuria [urinary albumin creatinine ratio (UACR below 30 mg\gm)].
- **Group (3):** 20 adult cases developing T2DM and microalbuminuria [UACR below 30 mg\gm].
- **Group (4):** 20 adult cases developing T2DM and macroalbuminuria (UACR over 300 mg\gm).

Inclusion criteria

We included adult cases developing T2DM.

Firstly, our team took a detailed history from all participants, then full clinical examination was conducted. Also, all subjects were investigated for routine lab testing, including [Complete blood count (CBC), fasting (FBG) and 2 hours post prandial plasma glucose (2HPPG), glycated hemoglobin (HbA1c), lipid profile tests, kidney function tests, complete urine analysis, UACR, liver function tests], specific laboratory investigations and radiological investigation.

Our team obtained blood samples in the morning following a fasting period of twelve hours. Collecting a blood portion was conducted on ethylenediaminetetraacetic acid (EDTA) in order to determine the HbA1c level. The remaining fraction is left to coagulate at ambient temperature. The serum was separated employing centrifuge with a speed of 3000 revolutions per minute for ten minutes. The resulting sera were split into several aliquots, then kept at a temperature of -70 °C until the assay was conducted.

Glucose levels were determined with a specialized glucose kit from Bioscience, Egypt, and analyzed utilizing a spectrophotometer instrument called URIT-810 from China. The TC levels as well as TG were determined utilizing an enzymatic colorimetric approach with specialized cholesterol and triglycerides kits from Spin react Spain. The analysis was conducted utilizing spectrophotometric devices. The concentration of high density lipoprotein (HDL-c) was determined with the HDLc precipitating reagent kit (Spin react, Spain) then underwent analysis with a spectrophotometer. Estimations were made for very low-density lipoprotein (VLDL-c) along with low-density lipoprotein (LDL-c).

The measurement of serum creatinine was conducted with a Creatinine (Colorimetric) kit. The serum uric acid measurement was conducted utilizing a uric acid uricase/peroxidase kit manufactured by Biosystems S.A., a company accredited for quality based on EN ISO 13485 as well as EN ISO 9001 standards. The company is located at Costa Brava, 30. 08030 Barcelona, Spain.

To measure UACR, morning urine samples were obtained and subjected to centrifuge with a speed of 1000 rpm/minute for ten minutes. The liquid portion was separated into tubes for biochemical examination. Measuring the concentration was conducted utilizing a solid phase enzyme linked immunosorbent assay (ELISA) employing a commercial test kit procured from DRG Diagnostics, USA, donated by Mogen Sen.

The serum AD level was quantified utilizing ELISA technology. Phoenix Pharmaceuticals, Inc., is a company based in the United States. The coefficients of variation (CVs) for intra-assay vary from 5% to 7%, while the CVs for inter-assay range from 12% to 15%. The assay's sensitivity is 0.3 ng/mL, and the detection limit falls between 0.01 ng/mL and 100 ng/mL.

The testing method used by the kit is a double-antibody sandwich ELISA, which is utilized for measuring the Human AD level in samples. Apply AD toto monoclonal antibody Enzyme to a pre-coated well containing Human AD monoclonal antibody. Incubate the mixture. Next, introduce AD antibodies that are labelled with biotin, and combine them employing Streptavidin-HRP for creating an immune complex. Repeat incubating and washing the mixture to eliminate any uncombined enzyme. Next, introduce Chromogen Solution A and B. As a result, the liquid undergoes a color transformation from its original state to blue. Finally, when exposed to acid, the color changes to yellow. There was a positive correlation between the color's chroma and the concentration of the Human Substance AD in the sample.

Test processes include the preparation of reagents, samples, as well as standards. Combine prepared samples and standards with antibodies that have been labelled with an enzyme. Allow them to react for 60 minutes at a temperature of 37 ℃. The plate was rinsed five times and then adding chromogen solution A as well as B was conducted. The reaction took place for 10 minutes at a temperature of 37 ℃. Implement a cessation solution. Obtain the optical density (OD) measurement within a time frame of 10 minutes, and thereafter do the necessary calculations.

Calculation: Plot the standard density on the horizontal axis and the OD value on the vertical axis to create a standard curve on graph paper. Determine the density corresponding to the sample optical density (OD) value by using the sample value. This will yield the sample density. Alternatively, calculate the equation of the straight line regression using the standard density and OD value of the standard curve. Then, use the sample OD value in equation to measure sample density.

Statistical analysis

Our team analyzed the data statistically utilizing SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were showcased through mean and standard deviation (SD) then the comparison among the all groups was conducted utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were illustrated through frequency and percentage (%). Analysis was implemented utilizing the Chi-square test. Pearson's correlation coefficient (r) test was utilized for correlating data. Receiver operating

characteristic (ROC curve) analysis was made for obtaining the most sensitive in addition to specific cut off value for AD. Logistic regression analysis was utilized in univariate along with multivariate of AD. P value of below 0.05 was deemed statistically significant.

Results

As regards age along with sex there was insignificant difference when comparing all studied groups (p= 0.537, and 0.531 respectively). Regarding disease duration, a significant variance was observed between the three groups. Diabetic groups without albuminuria have a significantly lower duration of disease than diabetic groups with microalbuminuria and diabetic groups with macroalbuminuria (P value = 0.001). Diabetic groups with microalbuminuria have significantly lower duration of disease than diabetic groups with macroalbuminuria. Table 1.

Table 1: Patient characteristics and lab data for all participants

		Group 1	Group 2	Group 3	Group4	p. value	Post Hoc
Age		59.75±8.02	60.45±7.92	61.2±7.32	63.15±7.40	0.537	-
Sex	Male	9 (45.0%)	99 (45.0%)	11 (55.0%	13 (65.0%)	0.531	-
	Female	11 (55.0%)	11 (55.0%)	9 (45.0%)	7 (35.0%)		
Duration of disease (Years)		-	7.20±1.88	9.70±2.05	11.10±1.77	<0.001*	P1=0.001* P2=0.001* P3=0.001*

Data are illustrated through mean ± SD or frequency (%).*: significant as P value equal to or below 0.05. P1: Group 2 & Group 3, P2: Group 2 & Group 4, P3: Group 3 & Group 4

Laboratory findings of all cases are illustrated on table 2 and 3.

Table 2: Comparison among all groups as regards laboratory findings

			p. value	Post Hoc
Fasting blood glucose (mg/dl)	Group 1	90.70±8.84	<0.001*	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.131
	Group 2	138.55±12.40		
	Group 3	173.25±20.12		
	Group 4	180.70±17.83		
Two- hour postprandial plasma glucose (mg/dl)	Group 1	130.20±9.90	<0.001*	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.729
	Group 2	242.45±18.45		
	Group 3	281.55±36.92		
	Group 4	284.05±16.17		
Glycated hemoglobin (per gm %)	Group 1	4.85±0.31	<0.001*	P1=0.001* P2=0.001* P3=0.001* P4=0.074 P5=0.001* P6=0.001*
	Group 2	7.96±0.91		
	Group 3	8.50±1.07		
	Group 4	9.48±1.19		
Albumin/ creatinine ratio (mg/g)	Group 1	10.84±3.85	<0.001*	P1=0.810 P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.131
	Group 2	15.46±2.86		
	Group 3	176.45±65.83		
	Group 4	489.05±101.57		
Cholesterol (mg/dl)	Group 1	160.40±23.97	<0.001*	P1=0.023* P2=0.004* P3=0.001* P4=0.541 P5=0.023* P6=0.091
	Group 2	184.50±45.25		
	Group 3	190.90±27.52		
	Group 4	208.70±30.92		
TG (mg/dl)	Group 1	115.85±31.00	<0.001*	P1=0.040* P2=0.001* P3=0.001* P4=0.049* P5=0.058 P6=0.938
	Group 2	139.80±40.45		
	Group 3	162.70±43.23		
	Group 4	161.80±27.81		
LDL-C (mg/dl)	Group 1	95.25±	<0.001*	P1=0.002* P2=0.015* P3=0.001* P4=0.483 P5=0.080 P6=0.015*
	Group 2	126.15±		
	Group 3	119.30±		
	Group 4	±		
HDL-C (mg/dl)	Group 1	41.30±4.77	0.247	-
	Group 2	40.05±9.14		
	Group 3	37.05±5.40		
	Group 4	38.95±7.00		

*: significant as P value equal to or below 0.05. FBG: Fasting blood glucose, 2HPPG: Two- hour postprandial plasma glucose, HbA1c: glycated hemoglobin. CHOL: Cholesterol, TG: Triglyceride, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein P1: Group one & Group two, P2: Group one & Group three, P3: Group one & Group four, P4: Group two & Group three, P5: Group two & Group four, P6: Group three & Group four

Table 3: Comparing among all groups as regards other laboratory findings

			p. value	Post Hoc
Creatinine (mg/dl)	Group 1	0.76±0.17	<0.001*	P1=0.459 P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.131
	Group 2	0.81±0.12		
	Group 3	1.24±0.22		
	Group 4	1.85±0.23		
BUN (mg/dl)	Group 1	11.00±1.92	<0.001*	P1=0.312 P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.729
	Group 2	12.00±1.38		
	Group 3	23.45±4.03		
	Group 4	33.30±4.11		
Serum uric acid (mg/dl)	Group 1	4.38±0.87	<0.001*	P1=0.016* P2=0.001* P3=0.001* P4=0.012* P5=0.064 P6=0.483
	Group 2	5.17±1.03		
	Group 3	5.99±0.98		
	Group 4	5.77±1.14		
Serum albumin (gm/dl)	Group 1	4.18±0.45	<0.001*	P1=0.063 P2=0.001* P3=0.001* P4=0.056 P5=0.001* P6=0.131
	Group 2	4.00±0.29		
	Group 3	3.81±0.22		
	Group 4	3.42±0.16		
AST (U/L)	Group 1	20.15±6.75	0.378	-
	Group 2	20.85±5.96		
	Group 3	21.15±9.20		
	Group 4	24.05±7.80		
ALT (U/L)	Group 1	21.30±7.45	0.961	-
	Group 2	20.30±9.14		
	Group 3	21.05±7.65		
	Group 4	20.15±7.80		
HB (gm/dl)	Group 1	14.13±0.67	<0.001*	P1=0.004* P2=0.015* P3=0.001* P4=0.001* P5=0.001* P6=0.200
	Group 2	13.38±0.91		
	Group 3	12.13±0.80		
	Group 4	11.81±0.78		
TLC (10^3 / UL)	Group 1	5.52±1.09	0.152	-
	Group 2	4.99±0.94		
	Group 3	5.52±0.98		
	Group 4	4.86±0.75		
PLT (10^3 / UL)	Group 1	299.20±47.77	0.411	-
	Group 2	431.75±635.97		
	Group 3	287.00±64.23		
	Group 4	284.05±75.42		

*: significant as P value≤ 0.05. BUN: Blood urea nitrogen. ALT: Alanine transaminase, AST: Aspartate aminotransferase. HB: Hemoglobin, TLC: Total leucocyte count, PLT: Platelets. P1: Group 1 & Group 2, P2: Group 1 & Group 3, P3: Group 1 & Group 4, P4: Group 2 & Group 3, P5: Group 2 & Group 4, P6: Group 3 & Group 4

As regard serum AD, a significant variance was observed between all groups. Control group has significant higher level of AD than diabetic group without albuminuria, diabetic group with microalbuminuria and diabetic group with macroalbuminuria (P value =0.001). Diabetic group without albuminuria has significant higher level of AD than diabetic group with microalbuminuria and diabetic group with macroalbuminuria (P value =0.001). Diabetic group with microalbuminuria has insignificant different level of AD when compared with diabetic group with macroalbuminuria. Table 4

Table 4: Comparison among all groups regarding serum adropin.

		Mean	P. value	Post hoc test
Adropin (Pg/ml)	Group 1	645.75±160.79	0.001*	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.531
	Group 2	354.65±150.27		
	Group 3	227.00±70.81		
	Group 4	203.45±51.26		

*: significant as P value≤ 0.05. P1: Group 1 & Group 2, P2: Group 1 & Group 3, P3: Group 1 & Group 4, P4: Group 2 & Group 3, P5: Group 2 & Group 4, P6: Group 3 & Group 4

A significant negative association was observed between serum AD and age (P value=0.001), duration of disease (P value=0.004),FBG (P value=0.001), 2HPPG (P value=0.001), HbA1c (P value=0.001), Albumin/creatinine (P value=0.001), cholesterol (P value=0.001), TG (P value=0.008), LDL (P value=0.001), creatinine (P value=0.001), blood urea nitrogen (BUN) (P value=0.001), uric acid (P value=0.001). A significant positive relationship was also noted among AD and HDL (P value=0.023), albumin (P value=0.001), Hb (P value=0.001). No association was observed between AD and aspartate aminotransferase (AST), alanine transaminase (ALT), total leucocyte count (TLC), along with platelets. Table 5.

Table 5: Association between Adropin and various parameters

	Adropin	
	r	P value
Age (Years)	-0.601	0.001*
Duration of disease(Year)	-0.363	0.004*
FBG	-0.737	0.001*
2HPPG	-0.745	0.001*
HbA1c	-0.720	0.001*
Albumin/ Creatinine	-0.609	0.001*
Cholesterol	-0.367	0.001*
TG	-0.294	0.008*
LDL	-0.406	0.001*
HDL	0.254	0.023*
Serum Creatinine	-0.583	0.001*
BUN	-0.620	0.001*
Serum uric acid	-0.464	0.001*
Serum albumin	0.607	0.001*
AST	-0.087	0.442
ALT	0.007	0.954
Hemoglobin	0.564	0.001*
Total leucocyte count	0.156	0.168
Platelet	-0.039	0.733

*: significant as P value≤ 0.05. r: Pearson correlation. FBG: Fasting blood glucose, 2HPPG: Two- hour postprandial plasma glucose, HbA1c: glycated hemoglobin, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine transaminase, HB: Hemoglobin, TLC: Total leucocyte count, PLT: platelets

AD can significantly predict diabetic nephropathy (P value < 0.001 and AUC = 0.907) at cut-off 225 with 90% sensitivity, 85% specificity, 86% PPV and 89% NPV. Figure 1

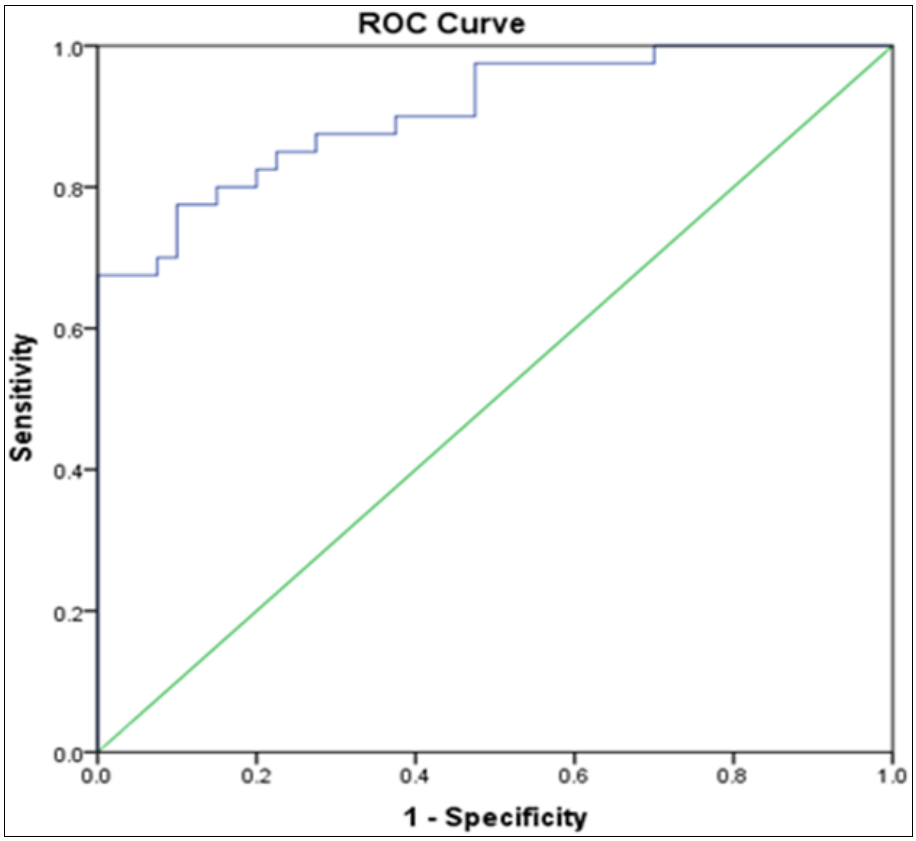

Fig 1: ROC curve of Adropin in prediction of diabetic nephropathy in type 2 diabetic patients.

Discussion

Type 2 diabetes mellitus (T2D) is a prevalent metabolic condition in Egypt [6]. Globally, DM has emerged as a complex pandemic due to factors such as population expansion, ageing, inactive lifestyle, obesity, uncontrolled urban development, industrialization, as well as environmental contamination. Affecting all body organs, it contributes to more financial costs on both individuals along with communities [7].

Similar to our findings, Ye *et al.* [8] also addressed no statistical variation regarding the gender distribution as well as mean age were among both DN and T2MD groups. Al

Shawaf et a. [9] reported increasing age towards the advanced complications from normoalbuminuria to micro to macroalbuminurea but without statistically significant differences.

Moreover, while comparing laboratory parameters for all groups, FBG as well as 2HPPG were significantly greater among diabetics in comparison to controls (P value= 0.001) and in albuminuria groups (3 and 4) than normal albuminuria group (2), while variance no significance among group 3 as well as group 4. HbA1c showed also significantly greater measurements among diabetic groups 2, 3, 4 in comparison to controls and within group 4 in comparison to group 2 in addition to group 3.

Supporting our findings, Shoukry *et al*. [10] and El-Horany *et al*. [11] addressed significant variances regarding FBG in addition to HbA1c among controls as well as T2DM groups as they exhibited reduced measurements within control group in comparison to diabetic group without albuminuria and diabetic groups with albuminuria.

Al Shawaf *et al*. [9] also in line to our findings reported that the mean diabetes duration in years increases from diabetic cases without albuminuria to diabetic cases with microalbuminuria to the diabetic cases with maccroaluminurea with also statistically increasing HbA1C (%) level from ($p \leq 0.001$) from controls to diabetic cases without albuminuria to the highest values in diabetic groups with albuminuria.

Xie *et al*. [12] also declared a statistically increasing HbA1C (%) level ($p \leq 0.001$) from control group to diabetic group without albuminuria to the highest values in diabetic groups with albuminuria. These results are in also conformity with those of Mahendran *et al*. [13] who stated that the duration of diabetes, the levels of FPG and HbA1c% exhibited significantly increased measurements within normoalbuminuria, microalbuminuria, along with macroalbuminuric diabetic groups in comparison with the healthy group and in macroalbuminuric diabetics in comparison to microalbuminuria, as well as normoalbuminuric diabetics.

Moreover, cholesterol, TG and LDL were significantly different among the four groups as there was elevation in lipid profile within diabetic groups in comparison to controls (P value <0.001) except for HDL that decreased in diabetic group than controls without statistically significant difference.

In concordance to our results, other researches show that worsening of diabetes is concomitant with deterioration of lipid profile as in (Shoukry *et al*. [10], Al Shawaf *et al*. [9].

This may be explained as Lipoprotein abnormalities are more prominent among individuals exhibiting high HbA1c levels. DN is a common cause of aberrant lipoprotein metabolism and may be affected by both renal function deficiency in addition to metabolic control of diabetes [14].

In our research, kidney functions as serum creatinine, BUN and uric acid showed greater measurements among diabetics with albuminuria in comparison to group without albuminuria than controls. In addition, albumin and hemoglobin exhibited significantly greater measurements among controls in comparison to the albuminuric groups but serum AST and ALT were insignificantly different among the four groups.

El-Horany *et al*. [11] also reported that both macroalbuminuric along with microalbuminuric diabetics showed significantly greater serum urea and serum creatinine levels in comparison to normoalbuminuric diabetics, as well as controls, with greater significant measurements found among macro albuminuric diabetics.

Al Shawaf *et al*. [9] also in agreement to our findings reported ACR level was increased in diabetic groups than control group with also a statistically significant elevation regarding serum creatinine as well as BUN while decrease in serum albumin in diabetic group with albuminuria than diabetic group without albuminuria than controls. This conclusion was similar to that one by El-Horany *et al*. [11], Sapkota *et al*. [15], and Azadi *et al*. [16].

Es-Haghi *et al*. [17] found also that the DN group exhibited greater blood urea, creatinine as well as albumin levels in comparison to those with no nephropathy in addition to controls.

What is more, our research's primary finding is decreased AD levels among group 4 in addition to group3 in comparison with group 2 as well as controls controls. A significant negative association among serum AD and duration of disease, FBG, 2HPPG, HbA1c, Albumin/ creatinine, cholesterol, TG, LDL, creatinine, uric acid was observed. Also, a significant positive association was noted among AD and HDL albumin, Hb. Concerning our study, AD can significantly predict diabetic nephropathy (AUC = 0.907) at cut-off point of 225 with 90% sensitivity, 85% specificity, 86% PPV and 89% NPV.

Recent research have shown that AD has positive benefits on enhancing the glucose homeostasis, managing dyslipidemia, reducing hyperinsulinemia linked with obesity, along with maintaining energy homeostasis. Clinical investigations have shown that serum AD levels are reduced in several disorders, including NAFLD, T2DM, DN, coronary atherosclerosis, hypertension, as well as polycystic ovary disease [18].

Similar to our results, Es-Haghi *et al*. [17] reported that serum AD levels showed significantly lower values among diabetics developing nephropathy in comparison to both controls along with diabetics without nephropathy. In addition, they also observed that serum AD levels showed an inverse correlation with FBS, HbA1c, urea, creatinine, LDL, as well as ACR. Furthermore, their research revealed a significant positive association among HDL and albumin. The researchers conducted ROC curve analysis to see if AD may serve as a new biomarker for differentiating DN from those without nephropathy as well as controls. The results showed a sensitivity of 80%, specificity of 60%, while an area under the curve exhibited 0.830.

A prior research conducted by by Hu and Chen, [19] aimed to assess the potential impact of AD levels on the DN development. It was found that T2DM cases developing nephropathy exhibited lower AD levels in comparison to others without nephropathy. Additionally, it addressed a correlation among AD levels and BUN, Creatinine, as well as ACR. After considering age and gender, a strong link was found between serum AD levels and BUN, CR, in addition to ACR. It was determined that serum AD levels are inversely related to renal function, which could be crucial in DN development.

AD may have a significant role in predicting CKD due to its strong association with the degree of endothelial dysfunction along with microvascular dysregulation. They are debated to be potential causes of kidney injury leading to CKD. Hence, AD may hinder the ability of endothelial cells to reduce DN by stimulating the generation of anti-

inflammatory substances in addition to nitric oxide (NO). Similarly, the mechanisms linked to the production and release of AD could be a crucial factor in DN pathophysiological progression [20].

The AD's metabolic capacities seem to have a safeguarding effect on the tubular system, irrespective of the eGFR changes. Therefore, the persistent renal ischemia may be improved by an increase in the AD synthesis. Consequently, higher peptide levels might be a marker of the activation of adaptive mechanisms, reducing the injury risks to focal organs. In contrast, low AD levels denotes a maladaptive change in energy homeostasis due to pro-inflammatory genes overexpression as well as excessive inflammatory cytokines production, reinforced by oxidative stress and mitochondria multifunction, which are caused by T2DM [20]. Additionally, several studies have proposed the hypothesis that AD may have a preventive function in the DN development by exerting anti-inflammatory actions. The specific function of AD in the mechanism of DN is yet uncertain. Inflammation exhibits a significant role in DN progression. The mRNA expression levels of TNF-α as well as IL-6 in diabetics' pancreas were significantly lowered by AD. The amount of circulating AD was shown to have a negative correlation with TNF-α levels among women developing PCOS [21].

After undergoing Roux-en-Y gastric bypass, there was a significant rise in plasma AD levels, indicating that reversal of the metabolic syndrome linked to obesity is also correlated with a reversal of low plasma AD levels [22].

Nevertheless, in disagreement with our findings, Hosseini *et al*., [23] addressed greater AD levels among cases developing T2DM, explained by the increased glucose levels or a response to anti-diabetic drugs. The variation between current findings as well as these ones could exist because of the varied demographics, diabetes duration, and / or therapy used.

Additionally, the variations among the findings could be due to the fact that beside the age, other factors involving underlying disorders like hypertension, elevated insulin resistance, NAFLD, along with endothelial dysfunction influence the AD serum levels [24]. More studies remain necessary to assess AD in clinical practice [25].

The limitations in our research include a modest sample size in addition to a single-center study. More multi-center research with large number participants is required to validate and characterize the function of AD in Diabetic patients and its consequences.

Conclusion

Serum AD level was significantly reduced among cases developing type 2 diabetes with microalbuminuria in comparison to controls or T2DM with normoalbuminuria or microalbuminuria. A significant negative association was noted between AD level and diabetes duration, HbA1c level, urine albumin/creatinine ratio along with serum creatinine. A positive association was also observed among AD and albumin, HB along with HDL. Serum AD may promise alternative serum marker in terms of predicting DKD patients from diabetics.

Financial support and sponsorship: Nil.

Conflict of Interest: Nil.

References

1. Noor T, Hanif F, Kiran Z, Rehman R, Khan MT, Haque Z, *et al*. Relation of copeptin with diabetic and renal function markers among patients with diabetes mellitus progressing towards diabetic nephropathy. Arch Med Res. 2020;51:548-55.
2. Pikkemaat M, Melander O, Bengtsson Boström K. Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. The Skaraborg Diabetes Register. J Diabetes Complications. 2015;29:1062-1065.
3. Sakin A, Sahin S, Behlul A, Sumnu A, Gursu M, Sakin A, *et al*. The association of visfatin levels with metabolic parameters and inflammation in diabetic nephropathy. Eur Phys J, 2020, 25.
4. Boric-Skaro D, Mizdrak M, Luketin M, Martinovic D, Tokic D, Vilovic M, *et al*. Serum adropin levels in patients on hemodialysis. Life (Basel), 2021, 11.
5. Bozic J, Borovac JA, Galic T, Kurir TT, Supe-Domic D, Dogas Z, *et al*. Adropin and inflammation biomarker levels in male patients with obstructive sleep apnea: A link with glucose metabolism and sleep parameters. J Clin Sleep Med. 2018;14:1109-1118.
6. Mohamed-Mohamed H, García-Morales V, Sánchez Lara EM, González-Acedo A, Pardo-Moreno T, Tovar-Gálvez MI, *et al*. Physiological Mechanisms Inherent to Diabetes Involved in the Development of Dementia: Alzheimer's Disease. Neurology International. 2023;15:1253-1272.
7. Maan HB, Meo SA, Al Rouq F, Meo IMU, Gacuan ME, Alkhalifah JM, *et al*. Effect of glycated hemoglobin (HbA1c) and duration of disease on lung functions in type 2 diabetic patients. Int J Environ Res Public Health; c2021. p. 18.
8. Ye B, Zhu X, Zeng Z, Ji X, Ji M. Clinical significance of serum homocysteine as a biomarker for early diagnosis of diabetic nephropathy in type 2 diabetes mellitus patients. Pteridines. 2021;32:11-16.
9. Al Shawaf E, Abu-Farha M, Devarajan S, Alsairafi Z, Al-Khairi I, Cherian P, *et al*. ANGPTL4: A predictive marker for diabetic nephropathy. J Diabetes Res. 2019;2019:4943191.
10. Shoukry A, Bdeer Sel A, El-Sokkary RH. Urinary monocyte chemoattractant protein-1 and vitamin D-binding protein as biomarkers for early detection of diabetic nephropathy in type 2 diabetes mellitus. Mol Cell Biochem. 2015;408:25-35.
11. El-Horany HE, Abd-Ellatif RN, Watany M, Hafez YM, Okda HI. NLRP3 expression and urinary HSP72 in relation to biomarkers of inflammation and oxidative stress in diabetic nephropathy patients. IUBMB Life. 2017;69:623-630.
12. Xie Y, Jin D, Qiu H, Lin L, Sun S, Li D, *et al*. Assessment of urinary podocalyxin as an alternative marker for urinary albumin creatinine ratio in early stage of diabetic kidney disease in older patients. Nefrologia (Engl Ed). 2022;42:664-670.
13. Mahendran KB, Bhaskar MV, Santha K, Inmozhi R, Perumal KK. Plasma and urinary type IV collagen levels for early detection of nephropathy in type 2 diabetes mellitus patients. Int J Health Sci (Qassim). 2016;10:492-498.
14. Barbagallo CM, Cefalù AB, Giammanco A, Noto D, Caldarella R, Ciaccio M, *et al*. Lipoprotein

abnormalities in chronic kidney disease and renal transplantation. Life (Basel), 2021, 11.
15. Sapkota S, Khatiwada S, Shrestha S, Baral N, Maskey R, Majhi S, *et al*. Diagnostic accuracy of serum cystatin c for early recognition of nephropathy in type 2 diabetes mellitus. Int J Nephrol. 2021;2021:8884126.
16. Azadi SM, Fadaei R, Omid-Shafaat R, Hosseini J, Moradi N. Elevated angiopoietin-like protein 3 serum levels in diabetic nephropathy patients and its association with renal function and lipid profile. BMC Nephrol. 2023;24:172.
17. Es-Haghi A, Al-Abyadh T, Mehrad-Majd H. The clinical value of serum adropin level in early detection of diabetic nephropathy. Kidney Blood Press Res. 2021;46:734-740.
18. Li N, Xie G, Zhou B, Qu A, Meng H, Liu J, *et al*. Serum adropin as a potential biomarker for predicting the development of type 2 diabetes mellitus in individuals with metabolic dysfunction-associated fatty liver disease. Front Physiol. 2021;12:696163.
19. Hu W, Chen L. Association of serum adropin concentrations with diabetic nephropathy. Mediators Inflamm. 2016;2016:6038261.
20. Berezina TA, Obradovic Z, Boxhammer E, Berezin AA, Lichtenauer M, Berezin AE, *et al*. Adropin predicts chronic kidney disease in type 2 diabetes mellitus patients with chronic heart failure. J Clin Med, 2023, 12.
21. Kume T, Calan M, Yilmaz O, Kocabas GU, Yesil P, Temur M, *et al*. A possible connection between tumor necrosis factor alpha and adropin levels in polycystic ovary syndrome. J Endocrinol Invest. 2016;39:747-754.
22. Faramia J, Ostinelli G, Drolet-Labelle V, Picard F, Tchernof A. Metabolic adaptations after bariatric surgery: adipokines, myokines and hepatokines. Curr Opin Pharmacol. 2020;52:67-74.
23. Shanaki M. Elevated serum levels of adropin in patients with type 2 diabetes mellitus and its association with insulin resistance insulin resistance; c2016.
24. Vase M, Taheri A, Hemmati M. The correlation between the serum level of adropin and blood pressure: A case-control study. Int Cardiovasc Res J, 2021, 15.
25. 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 Des Devel Ther. 2021;15:589-600.

How to Cite This Article
Huntsh AA, Elhoseny SA, Elkholy RA, Elbedewy TAE. Serum adropin as a biomarker of diabetic nephropathy in type 2 diabetic patients. International Journal of Advanced Research in Medicine. 2024;6(3):36-43.