Original Article

# Kidney Dysfunction Prediction by Serum Adropin in Type 2 Diabetes Iraqi Patients

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## Abstract

**Background:** Diabetic nephropathy (DN) is a problem that arises from microvascular complications with type 2 diabetes mellitus (T2DM). It especially denotes the deterioration of renal function. Adropin, a regulatory peptide hormone, has attracted interest for its potential role in regulating metabolism, specifically glucose metabolism and insulin resistance. **Objective:** To assess Adropin's role in the identification and severity of T2DM nephropathy. **Methods:** A cross-sectional study which involved an 88 patients with DN was conducted in the National Diabetes Center/Mustansiriyah University during the period from October 2023 to April 2024. Body mass index, blood analysis for sugar levels, lipid profile, renal function test, and albumin to creatinine ratio in urine were conducted. In addition, the content of human adropin was evaluated using an enzyme-linked immunosorbent assay. **Results:** Much more fasting blood sugar, glycated hemoglobin, insulin, homeostasis model assessment insulin resistance, cholesterol, triglycerides, low-density lipoprotein (LDL) and very LDL, urea, and creatinine were found in the microalbuminuria and macroalbuminuria groups of DN patients than in the normoalbuminuria group. The amount of adropin in the blood was lowered in people with microalbuminuria and macroalbuminuria (245.91 ± 59.47 and 179.86 ± 51.96 pg/ml, respectively) than in people with normoalbuminuria (377.97 ± 98.69 pg/ml) as well. While the subject attempts to identify the difference between the groups of DN, adropin works very well and is very sensitive. **Conclusion:** This study establishes a correlation between reduced adropin levels and impaired kidney function in individuals diagnosed with T2DM. Adropin content in the serum is able to serve as a biomarker for the early recognition of DN, by its role in glucose metabolism and insulin resistance.

**Keywords:** Adropin, biomarkers, diabetic nephropathy, type 2 diabetes mellitus

## Introduction

Diabetic nephropathy (DN) can be defined by a number of changes in various renal structures, including arteries, arterioles, kidney glomeruli, and tubules. Furthermore, it is characterized by the development of glomerular hypertension, which frequently results in the development of diffuse or nodular glomerulosclerosis, which eventually leads to chronic renal failure.[1] Until recently, albuminuria was considered a significant determinant in the development of glomerular injury, functioning as a basic structure in the process.[2] Three distinct phases comprise the progression of DN: normoalbuminuria, microalbuminuria, and macroalbuminuria. Albuminuria is also linked to a reduction in blood pressure, hyperglycemia, and glomerular filtration rate (GFR), which is proportionate to albumin excretion, albuminuria reflects functional and potentially reversible abnormalities initiated by glomerular hyperfiltration, proteinuria, and size selective dysfunction.[3] Other factors that may lower GFR include female gender, fat accumulation, and high triglycerides. This clarifies the reason for DN's phenotypic lack of correlation with its histological abnormalities, given the many reasons that cause it. This disease's development requires new biomarkers to improve diagnosis, evaluation, response to therapy, and prognosis. These abnormalities are not limited to DN.[4] Adropin is a peptide hormone mostly found in the brain and liver. The origin of this can be traced back to a preceding gene that was

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encoded by the energy homeostasis-associated gene (ENHO).[5] Adropin exerts its effects by binding to numerous receptors located in distinct organs. After the discovery of adropin, researchers originally concentrated on its role in lipid and carbohydrate metabolism, as well as its correlation with insulin resistance.[6,7] The pancreas acinar cells and islets of Langerhans cell capillaries were shown to contain adropin. Impaired insulin secretion is one of the most recent findings suggesting that adropin may have a role in controlling the activities of pancreatic beta cells.[8] Adropin may directly induce microangiogenesis, microvessel density, oxidative stress, myocardial fibrosis, and mortality but not glucose and lipid metabolism. Adropin stimulates phosphor-endothelial nitric oxide synthase expression and suppresses transforming growth factor β1, NADPH oxidase 4, and cleaved caspase 3 expression.[9]

## Methods

### Study design

Patients diagnosed with type 2 diabetes mellitus (T2DM) who visited the National Diabetes Center (NDC) at Mustansiriyah University during October 2023 and May 2024 were the subjects of a study that focused on cross-sectional data collection. All participants in the study provided their written informed consent, and a total of 88 patients were included in the analysis (33 samples of normoalbuminuria and 55 samples of microalbuminuria and macroalbuminuria, depending on their availability). Exclusion in the study was dependent on the absence of smoking, cancer, gestational diabetes, type 1 diabetes, cardiovascular disease, or any other comorbidity. Patients were categorized into three groups based on their urine albumin-to-creatinine ratio (ACR): normoalbuminuria, microalbuminuria, and macroalbuminuria. The normoalbuminuria group consisted of patients with a urinary ACR <30 mg/g creatinine; microalbuminuria included patients with an ACR between 30 and 300 mg/g creatinine; and macroalbuminuria included patients with an ACR >300 mg/g creatinine.

### Sample collection

The collection of fasting blood samples occurred from the antecubital vein of all patients. Immediately, the serum was separated by draining it into plain tubes using a 5 ml disposable syringe. The tubes were then allowed to sit at the room temperature (25°C) for 15 min before being centrifuged at 2000–3000 rpm for 10 min. The objects were melted and kept at a frozen temperature to avoid repeated freezing. Several factors were tested using serum aliquots in the study. We used the enzyme-linked immunosorbent assay (ELISA) kits made in the USA for these measurements, which are an ELISA, or enzymatic spectrophotometric method. All assays matched the directions provided by the manufacturer. Patients' urine samples were analyzed to test the ACR.

### Ethical issues

The scientific committees of the Chemistry and Biochemistry Department and NDC of Al Mustansiriyah University confirmed their approval of this study. All patients have the right to withdraw at any moment they feel like it, and verbal agreement was acquired when the goals and procedures were described to them.

### Statistical analysis

Data analysis was done by utilizing SPSS for Windows, version 25 (SPSS Inc. Chicago, Illinois, United States). Shapiro–Wilk normality test was used to determine whether the studied parameters followed a gaussian distribution. Once the data followed a normal distribution by itself, the mean and standard deviation were employed to display it. Whether group means varied significantly was determined using the analysis of variance. Less than 0.05 was considered statistically significant. We investigated the sensitivity, specificity, and area under the curve (AUC) of all adropin values in the study category. Adropin's ability to identify normoalbuminuria, microalbuminuria, and macroalbuminuria was tested. For diagnostic sensitivity and specificity, the best threshold was used.

## Results

When comparing the several groups with type 2 DN (normoalbuminuria, microalbuminuria, and macroalbuminuria), it was found that adropin exhibited substantial differences within the groups ($P < 0.001$), as depicted in Figure 1. Furthermore, the fasting blood sugar (FBS), lipid profile, and renal function tests also revealed a notable discrepancy among individuals with type 2 DN ($P < 0.05$). The findings are presented in Table 1.

Table 2 demonstrates that adropin exhibited negative correlations with FBS in patients from the normoalbuminuria group ($P = 0.018$, $r_p = -0.468$) and substantial positive correlations with high-density lipoprotein (HDL) in patients from the microalbuminuria group ($P = 0$, $r_p = 0.701$).

In order to differentiate between DN in the normoalbuminuria group, microalbuminuria group, and macroalbuminuria group, the parameter should be adjusted based on the AUC that can be achieved and whether this achievement is statistically significant or not. Table 3 displays the findings of the AUC for the optimal cutoff values of adropin that accurately

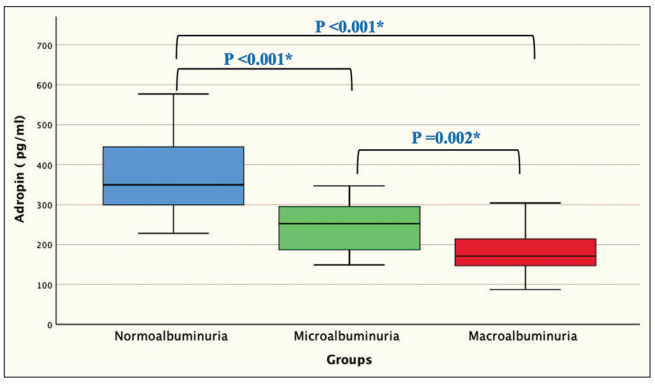


**Figure 1:** Boxplot of adropin (pg/ml) in the study groups

**Table 1: Clinical measures and baseline laboratory tests of diabetic nephropathy patients**

| Variables | Type 2 diabetes groups | Mean±SD | *P* value ANOVA test |
|---|---|---|---|
| FBS (mg⁄dL) | Normoalbuminuria | 173.72±39.02 | <0.001* |
| | Microalbuminuria | 195.78±34.42 | |
| | Macroalbuminuria | 224.05±37.26 | |
| HbA1c (%) | Normoalbuminuria | 8.42±1.17 | 0.002* |
| | Microalbuminuria | 8.9±1.33 | |
| | Macroalbuminuria | 9.62±0.99 | |
| Insulin (U⁄mL) | Normoalbuminuria | 7.95±2.54 | <0.001* |
| | Microalbuminuria | 10.94±2.61 | |
| | Macroalbuminuria | 14.7±4.95 | |
| HOMA_IR | Normoalbuminuria | 3.2±1.1 | <0.001* |
| | Microalbuminuria | 5.25±1.72 | |
| | Macroalbuminuria | 7.8±1.75 | |
| Cholesterol (mg⁄dL) | Normoalbuminuria | 211.76±11.44 | <0.001* |
| | Microalbuminuria | 234.56±10.59 | |
| | Macroalbuminuria | 246±9.41 | |
| Triglyceride (mg⁄dL) | Normoalbuminuria | 205.36±12.53 | <0.001* |
| | Microalbuminuria | 228.8±12.45 | |
| | Macroalbuminuria | 251.29±9.3 | |
| HDL (mg⁄dL) | Normoalbuminuria | 44.04±3.16 | <0.001* |
| | Microalbuminuria | 40.64±2.27 | |
| | Macroalbuminuria | 39.38±2.89 | |
| LDL (mg⁄dL) | Normoalbuminuria | 114.12±12.45 | <0.001* |
| | Microalbuminuria | 158±9 | |
| | Macroalbuminuria | 171.81±6.33 | |
| VLDL (mg⁄dL) | Normoalbuminuria | 32.88±3.37 | <0.001* |
| | Microalbuminuria | 38.04±3.35 | |
| | Macroalbuminuria | 45.43±5.87 | |
| Blood urea (mg/dL) | Normoalbuminuria | 30.69±3.56 | <0.001* |
| | Microalbuminuria | 38.79±2.12 | |
| | Macroalbuminuria | 45.86±2.21 | |
| Serum creatinine (mg/dL) | Normoalbuminuria | 0.83±0.11 | <0.001* |
| | Microalbuminuria | 0.96±0.15 | |
| | Macroalbuminuria | 1.63±0.18 | |
| GFR (mL/min/1.73 $m^2$) | Normoalbuminuria | 90.98±17.06 | <0.001* |
| | Microalbuminuria | 84.99±20.98 | |
| | Macroalbuminuria | 46.84±7.77 | |

*GFR (mL/min/1.173 $m^2$)=186×creatinine (serum) − 1.154 × age−0.203 × 0.742 (if female). GFR: Glomerular filtration rate, FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, HOMA-IR: Insulin resistance, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very LDL

identified the normoalbuminuria group compared to the macroalbuminuria groups. The adropin test yielded a high AUC value of 0.979, with a cutoff value of <248.5 pg/mL. The test demonstrated a sensitivity of 0.96 and a specificity of 0.91.

## Discussion

In this study, adropin, a hormone, was measured and the results showed a high significant difference in mean (P < 0.001) for normoalbuminuria and microalbuminuria compared to macroalbuminuria groups, [Table 4]. This result is consistent with Li *et al*.[10] and Jasaszwili *et al*.[11] in which research indicated that adropin levels decreased sharply in those with diabetes. These findings match previous research that linked a decline in adropin levels to an increased risk of renal impairment in type 2 diabetic individuals.[12] The advantageous impacts of adropin have been explained through the enhancement of glucose oxidation and the sensitization of insulin signaling pathways.[13] Adropin appears to induce glucose oxidation in muscle cells by increasing GLUT4 cell-surface expression and insulin-mediated AKT phosphorylation. Shelest and Buriakovska[13] concluded that DN patients had statistically lower adropin.[14] Diabetes-related chronically active immune systems and low-grade inflammation may cause DN. Diabetes patients have higher levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-8 in their renal tissue, they strongly correlate with albuminuria in diabetics. Also cause glomerular basement membrane thickening, endothelial permeability, apoptosis, and renal cell toxicity.[14] It has

**Table 2: Pearson correlation coefficient between adropin ( pg/mL) and other variables in three different groups**

| Variables | Patients groups | | | | | |
|---|---|---|---|---|---|---|
| | Type 2 diabetes with normoalbuminuria group | | Type 2 diabetes with microalbuminuria group | | Type 2 diabetes with macroalbuminuria group | |
| | $r_p$ | *P* | $r_p$ | *P* | $r_p$ | *P* |
| FBS (mg⁄dL) | −0.468* | 0.018 | −0.036 | 0.864 | −0.095 | 0.683 |
| HbA1c (%) | 0.179 | 0.392 | −0.052 | 0.805 | 0.122 | 0.6 |
| Insulin (U⁄mL) | 0.021 | 0.92 | −0.041 | 0.845 | −0.048 | 0.836 |
| IR (HOMA_IR) | −0.319 | 0.12 | −0.018 | 0.931 | −0.174 | 0.45 |
| Cholesterol (mg⁄dL) | 0.177 | 0.397 | 0.012 | 0.954 | −0.237 | 0.301 |
| Triglyceride (mg⁄dL) | −0.25 | 0.229 | −0.284 | 0.169 | 0.241 | 0.293 |
| HDL (mg⁄dL) | 0.086 | 0.683 | 0.701** | 0 | −0.354 | 0.115 |
| LDL (mg⁄dL) | −0.232 | 0.264 | 0.268 | 0.195 | 0.12 | 0.605 |
| VLDL (mg⁄dL) | −0.07 | 0.74 | −0.182 | 0.383 | -0.397 | 0.075 |
| Adropin (pg⁄mL) | 1 | - | 1 | - | 1 | - |
| Blood urea (mg/dL) | −0.176 | 0.4 | −0.251 | 0.227 | 0.041 | 0.859 |
| Serum creatinine (mg/dL) | 0.107 | 0.609 | 0.179 | 0.393 | −0.091 | 0.693 |
| GFR (mL/min/1.73 $m^2$) | −0.049 | 0.818 | −0.205 | 0.325 | 0.079 | 0.733 |

*Significant correlation (*P*<0.05), **High significant correlation (P<0.01). FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, HOMA-IR: Insulin resistance, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very LDL, GFR: Glomerular filtration rate

**Table 3: Analysis of area under curve for diagnosis efficacy and prediction capability of adropin between groups**

| Combination | Parameter | Cut off | SE | SP | AUC | Se | 95% | *P* |
|---|---|---|---|---|---|---|---|---|
| Normoalbuminuria versus microalbuminuria | Adropin | <295.5 | 0.84 | 0.68 | 0.842 | 0.054 | 0.735–0.948 | <0.001* |
| | GFR | <83.75 | 0.60 | 0.66 | 0.606 | 0.088 | 0.433–0.780 | 0.197 |
| Normoalbuminuria versus macroalbuminuria | Adropin | <248.5 | 0.96 | 0.91 | 0.979 | 0.019 | 0.942–1.000 | <0.001* |
| | GFR | <80.3 | 0.72 | 0.82 | 0.840 | 0.073 | 0.696–0.984 | <0.001* |
| Microalbuminuria versus macroalbuminuria | Adropin | <187.5 | 0.88 | 0.68 | 0.877 | 0.052 | 0.775–0.979 | <0.001* |
| | GFR | <62.4 | 0.80 | 0.76 | 0.791 | 0.071 | 0.653–0.930 | 0.001* |

*Be significant (p<0.05), GFR: Glomerular filtration rate, SE: Sensitivity, SP: Specificity, Se: Standard error, AUC: Area under curve

**Table 4: Adropin level in diabetic nephropathy groups**

| Variables | Type 2 diabetes groups | Mean±SD | SE | Median | *P* value ANOVA test |
|---|---|---|---|---|---|
| Adropin (pg/mL) | Normoalbuminuria | 377.97±98.69 | 17.45 | 349.5 | <0.001* |
| | Microalbuminuria | 245.91±59.47 | 10.35 | 252 | |
| | Macroalbuminuria | 179.86±51.96 | 11.08 | 171 | |

*Significant difference between groups (*P*<0.05). SD: Standard deviation, SE: Standard error, ANOVA: Analysis of variance

been stated that low concentration of adropin plays a significant role in the development of DN, as its lack is linked to increased levels of TNF-α, IL-1, IL-6, and highly sensitive C-reactive protein.[13] Adropin is thought to lower the levels of the PDH kinase gene, which in turn lowers its inhibitory effect on the pyruvate dehydrogenase complex and raises glycolysis.[15] Adropin levels in the blood may influence skeletal muscle metabolism by affecting fuel selection preference for glucose oxidation in the fed state. Adropin controls hepatic lipogenic gene expression and the PPARγ receptor, a vital regulator of lipogenesis.[16] The lipid profile displayed in Table 1 demonstrates statistically significant discrepancies in cholesterol, triglyceride, HDL, low-density lipoprotein (LDL), and very LDL (VLDL) levels among the groups under investigation. Dyslipidemia is a common metabolic modification associated with diabetes. It is characterized by a wide range of lipid abnormalities that are collectively known as diabetic dyslipidemia. These abnormalities include high levels of triglycerides, low levels of HDL cholesterol, and a shift toward small, dense LDL cholesterol. This pathogenic trio is commonly seen in patients with diabetes mellitus.[17] Insulin resistance impairs the ability of lipoprotein lipase (LPL) to break down extremely LDL and other triglyceride-rich particles into free fatty acids. The end effect is the elevated levels of triglycerides in the bloodstream due to the reduced action of LPL.[18] Finally, all of these defects lead to higher levels of VLDL, triglycerides, and LDL, along with lower levels of HDL. This is what diabetic dyslipidemia appears to be like.[17] A family with T2DM had three generations of ENHO gene mutations (the adropin gene). These generations had considerably lower blood adropin levels and regulatory T-cells in T2DM family

members. Adropin insufficiency was significantly linked to regulatory T-cell shortages. The invasion of visceral adipose tissue by proinflammatory macrophages is thought to cause inflammation and insulin resistance. Adropin reduces adipose tissue inflammation and improves insulin sensitivity. Thus, adropin deficiency could result in T2DM.[19] Adropin increases glycolytic flow through both oxidative and nonoxidative mechanisms and reduces skeletal muscle fatty acid intake through the expression of the sarcolemmal fatty acid translocase, therefore enhancing the flexibility of metabolic balance.[20] According to Table 1, the renal function test results reveal substantial differences ($P < 0.001$) in serum urea, creatinine, and GFR among all groups. Variations in current and previous estimated GFRs are the key predictors of DN development. The GFR is the principal clinical biomarker for DN prognosis and is used in clinical practice and research studies. Current diagnostic and follow-up procedures are less useful for normoalbuminuric patients, who are becoming more common and lack tailored treatment. Due to the limits of current diagnostic and follow-up approaches in normoalbuminuric individuals, additional DN biomarkers are needed.[21] The results of the FBS, insulin, and homeostasis model assessment insulin resistance analyses were highly significant ($P < 0.001$) and indicated there were the significant differences among groups [Table 1]. The results of the data of the DN patients (macroalbuminuria) were significantly higher than the other two groups, and the data of the microalbuminuria patients was also higher than the data of the normoalbuminuria group. This result confirmed the clinical diagnosis of DM patients. Furthermore, this result was agreed by,[22] that fasting hyperglycemia affects practically all diabetics, possibly due to a hormonal imbalance that increases hepatic glucose transport. Increased glucose transport causes an imbalance in glucose homeostasis, such as impaired liver insulin sensitivity, which increases the production of glucose in the liver and decreases peripheral glucose consumption. The main strength of the study, that the results provided new insights into the possible role of serum adropin in pathophysiology of cardiovascular risk in T2DM, while the limitations of the study, first the sample size was not sufficiently large to achieve definitive conclusions. Second, it is a cross-sectional design. Hence, the causative relation must be confirmed by the future longitudinal studies.

## Conclusion

The results of this study indicate that a decrease in adropin could potentially be used as a predictive factor for a decline in kidney function in future. In addition, adropin may have a role in the underlying mechanisms of DN and its related consequences.

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### Conflicts of interest

There are no conflicts of interest.

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