

# Assessment of serum adropin level in type 2 diabetic patients with or without nephropathy

Mohamed E. Ibrahim<sup>a</sup>, Dalia N. El-Din<sup>b</sup>, Ahmad M.F. Alkot<sup>a</sup>,  
Ahmed E. Mansour<sup>a</sup>, Hasan G.A. Amer<sup>a</sup>

Departments of <sup>a</sup>Internal Medicine, <sup>b</sup>Clinical & Chemical Pathology, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence to Ahmad M.F. Alkot, MBCh, Dahtora, Zifta, Algharbeia Governorate, 31654, Egypt. Tel: 00201032173909; e-mail: dr.ahmadalkot@gmail.com

**Received:** 28 November 2020

**Revised:** 5 January 2021

**Accepted:** 15 January 2021

**Published:** xx xx 2020

**Journal of The Arab Society for Medical Research** 2021, 16:17–23

## Background/aim

Diabetes predisposes the affected individual to long-term macrovascular and microvascular complications. Renal complications represent a major turning point in the life of people with diabetes. Adropin is a peptide primarily secreted by the liver and brain. It is encoded by the Energy Homeostasis Associated gene (Enho). Adropin main function is to prevent insulin resistance, dyslipidemia, and impaired glucose tolerance. This study aimed to assess the serum adropin level in patients with type 2 diabetes mellitus (T2DM) and diabetic nephropathy (DN).

## Patients and methods

This case–control study was conducted on 50 diabetic patients from Inpatient and Outpatient Clinics of Internal Medicine Department, Benha University Hospitals, Egypt, in addition to 25 apparently healthy controls. Upon their informed consent, and after complete history taking and full clinical examination, blood samples were taken for biochemical analysis and serum adropin level measurement. Adropin was measured using enzyme-linked immunosorbent assay technique. Fasting and 2-h postprandial blood glucose, glycated hemoglobin, blood urea, serum creatinine, and glomerular filtration rate were done.

## Results

This study demonstrated that adropin shows significant reduction in the diabetic group when compared with the control group and also exhibits significant decline in the DN group when compared with the diabetic group. There was a significant negative correlation between adropin and T2DM duration as well as with glycated hemoglobin ( $r=-0.552$  and  $-0.467$ , and  $P=0.001$  and  $0.001$ , respectively). Moreover, there was a significant positive correlation between adropin and estimated glomerular filtration rate ( $r=0.358$  and  $P=0.002$ ).

## Conclusion

Adropin is significantly reduced in T2DM when compared with normal participants, and the reduction of adropin is correlated with the deterioration in kidney functions manifested by the reduction in estimated glomerular filtration rate. These findings suggested that the reduction of serum adropin may play a role in the pathogenesis of T2DM and DN.

## Keywords:

adropin, diabetic nephropathy, estimated glomerular filtration rate, type 2 diabetes mellitus

J Arab Soc Med Res 16:17–23

© 2021 Journal of The Arab Society for Medical Research  
1687-4293

## Introduction

Diabetes is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. This predisposes the affected individual to long-term macrovascular and microvascular complications [2]. Renal complications represent a major turning point in the life of people with diabetes. In type 2 diabetes, nephropathy is associated with increased cardiovascular mortality and morbidity [3].

Adropin is a novel bioactive protein encoded by Enho gene, and this metabolic hormone serves to modulate lipid and glucose metabolism and to maintain insulin sensitivity [4]. In the experimental studies, systemic injections of adropin have been shown to

improve skeletal muscle insulin sensitivity and to promote weight loss. Adropin has been shown in the literature to be decreased in many diseases, such as type 2 diabetes mellitus (T2DM), coronary atherosclerosis, and polycystic ovary disease [5]. The aim of this work was to evaluate and compare the level of adropin in healthy participants, and in type 2 diabetic patients with or without nephropathy.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

## Patients and methods

### Patients

This case-control study was conducted on 75 participants, comprising 50 patients with T2DM and 25 apparently healthy age matched controls, from Inpatient and Outpatient Clinics of Internal Medicine Department, Benha University Hospitals, Qalyubiyya Governorate, Egypt.

### Inclusion criteria

Participants with age between 35 and 70 years were included in the study.

The diagnosis of DM was made in accordance with the American Diabetic Association criteria, which include a fasting plasma glucose level of 126 mg/dl or higher, or 2-h postprandial plasma glucose level of 200 mg/dl or higher, or a random plasma glucose of 200 mg/dl or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or glycated hemoglobin (HbA1C) level of 6.5% or higher in type 2 diabetic patients without diabetic nephropathy (DN). DN was defined as a rise in urinary albumin-creatinine ratio (UACR >30 mg/g) and reduced renal function, as reflected by raised plasma creatinine concentration, reduced calculated creatinine clearance, or decreased estimated glomerular filtration rate (eGFR <90 ml/min/1.73 m<sup>2</sup>) in diabetic patients [6].

### Exclusion criteria

Patients with causes of renal impairment other than DM such as autoimmune diseases, urinary tract infection, drugs, and urinary tract obstructive lesions were excluded. Pregnant women were also excluded as renal hyperfiltration during pregnancy decreases the accuracy of creatinine clearance and eGFR according to Koetje *et al.* [7].

### Study design

All participants are divided into three groups as follows:

Control group: 25 apparently healthy participants.

T2DM group: 25 type 2 diabetic patients with normal UACR, normal serum creatinine level, and normal eGFR.

Type 2 DN: 25 type 2 diabetic patients with UACR more than 30 mg albumin/g creatinine, abnormal serum creatinine level (>1.1 mg/dl in females and >1.2 mg/dl in males), and eGFR less than 90 ml/min/1.73 m<sup>2</sup> of body surface area [6].

### Ethical approval

All participants gave informed consent before being included in the study. The protocol was approved by the local institutional ethical committee of Benha Faculty of Medicine with approval no. M5-13-1-2020.

### Methods

After complete history taking and full clinical examination, age in years, duration of DM in years, sex distribution, BMI (kg/m<sup>2</sup>), as well as presence and absence of hypertension were recorded.

### Blood sampling

Overall, 7 ml of venous blood was withdrawn by a sterile vein puncture; 1 ml was transferred into a sterile tube containing EDTA and stored at 4°C till being used for HbA1C analysis, and the remaining 6 ml was transferred into a dry sterile centrifuge tube, then the whole blood was allowed to clot at room temperature for 30 min, and then centrifuged for 10 min at 4000 rpm. The clear supernatant serum was separated and 300 µl was kept frozen at -20°C till analysis of serum adropin, whereas the remaining serum was used for other biochemical analyses.

### Biochemical assessment

- (1) Fasting and 2-h postprandial blood glucose levels have been assessed by colorimetric method using kits of Cayman Chemical Co. (Ann Arbor, Michigan, USA) according to Braham and Trinder [8].
- (2) HbA1C was done according to the method of Zander *et al.* [9], using kits of My Bio Source Co (San Diego, California, USA).
- (3) Blood urea and serum creatinine have been done by colorimetric method, using kits of Sigma-Aldrich Co. (Saint Louis, Missouri, USA) according to Gutmann and Bergmeyer [10] and Fossati *et al.* [11], respectively.
- (4) GFR was estimated by modified diet for renal disease formula [7]:

$$\begin{aligned} \text{eGFR (ml/min/1.73m}^2\text{Entity is missing)} \\ = 175(\text{serum creatinine})^{-1.154}(\text{Age})^{-0.203} \\ (0.742 \text{ if female})(1.212 \text{ if African American}) \end{aligned}$$

Adropin was done using enzyme-linked immunosorbent assay kits for Human Adropin from Bioassay Technology Laboratory (Edgbaston, Birmingham, England) according to the instructions included with the kits.

### Statistical analysis

Collected data were analyzed using SPSS, version 17 (IBM, 590 Madison Avenue, New York, USA). Quantitative data were represented as means $\pm$ SD and 'one-way analysis of variance' was used to compare these means and test for significant differences. Qualitative data were expressed as percentage and tested for significant differences using  $\chi^2$  test. Spearman's correlation coefficient ( $r$ ) was used to evaluate the linear association between adropin and other variables. MedCalc statistical computer program 19.3.1 (MedCalc Software Ltd, Acaciaaan, Ostend, Belgium) was used to build receiver operating characteristic curves [12].

### Results

The data presented in Table 1 summarize the results of the study regarding age in years, duration of DM in years, sex distribution, BMI (kg/m<sup>2</sup>), and presence and absence of hypertension.

Both fasting and 2-h postprandial blood glucose (in mg/dl) levels were significantly higher ( $P\leq 0.05$ ) in T2DM and DN groups when compared with control group. HbA1C (as percentage) was significantly elevated

( $P\leq 0.05$ ) in T2DM group and DN group when compared with control group. Moreover, HbA1C was significantly higher ( $P\leq 0.05$ ) in T2DM group than DN group. Urea, creatinine (in mg/dl), and eGFR (in ml/min/1.73 m<sup>2</sup> of body surface area) were significantly lower in DN group when compared with normal and T2DM groups.

The study also showed that serum adropin level is significantly decreased in DN group when compared with control and diabetic groups. Moreover, it showed significant reduction in diabetic group when compared with control group (Table 2).

In the present study, there was a significant ( $P=0.001$ ) negative correlation between serum adropin level and T2DM duration, with a correlation factor ( $r$ )=-0.552 (Fig. 1).

Moreover, there was a significant ( $P=0.001$ ) negative correlation between serum adropin level and HbA1C, with a correlation factor ( $r$ )=-0.467 (Fig. 2).

On the contrary, there was a significant ( $P=0.002$ ) positive correlation between serum adropin level and eGFR, with a correlation factor ( $r$ )=0.358 (Fig. 3).

**Table 1 Demographic and clinical data of the studied groups**

| Parameters                     | Groups                      |                             |                             |
|--------------------------------|-----------------------------|-----------------------------|-----------------------------|
|                                | Control group               | T2DM group                  | DN group                    |
| Age (years)                    | 41.9 $\pm$ 7.4 <sup>a</sup> | 53 $\pm$ 10.2 <sup>b</sup>  | 58.1 $\pm$ 7.3 <sup>c</sup> |
| T2DM duration (years)          | 0                           | 7.3 $\pm$ 5.6 <sup>b</sup>  | 13.8 $\pm$ 6.9 <sup>c</sup> |
| Male [n (%)]                   | 13 (52)                     | 19 (76)                     | 21 (84)                     |
| Female [n (%)] <sup>a</sup>    | 12 (48) <sup>a</sup>        | 6 (24) <sup>b</sup>         | 4 (16) <sup>b</sup>         |
| BMI (kg/m <sup>2</sup> )       | 28 $\pm$ 2.8 <sup>a</sup>   | 29.2 $\pm$ 4.4 <sup>a</sup> | 29.7 $\pm$ 6 <sup>a</sup>   |
| HTN (+ve) [n (%)]              | 0                           | 9 (36)                      | 18 (72)                     |
| HTN (-ve) [n (%)] <sup>a</sup> | 25 (100) <sup>a</sup>       | 16 (64) <sup>b</sup>        | 7 (28) <sup>c</sup>         |

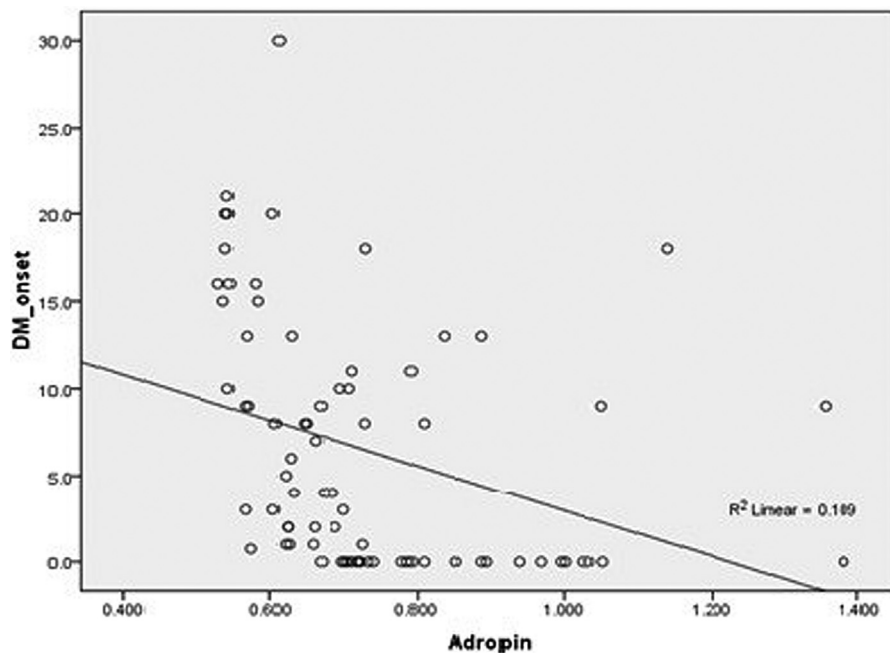
Data are represented as mean $\pm$ SD. DN, diabetic nephropathy; HTN, hypertension; T2DM, type 2 diabetes mellitus. <sup>a</sup> $\chi^2$  test. All different letters (a, b, c) in same row are significant at  $P$  value less than or equal to 0.05, using analysis of variance or  $\chi^2$  tests.

**Table 2 Blood glucose, glyated hemoglobin, Urea, Creatinine, estimated glomerular filtration rate, and adropin levels in the studied groups**

| Parameters                         | Groups                          |                                 |                                |
|------------------------------------|---------------------------------|---------------------------------|--------------------------------|
|                                    | Control group                   | T2DM group                      | DN group                       |
| Fasting blood glucose (mg/dl)      | 76.8 $\pm$ 10.7 <sup>a</sup>    | 207.4 $\pm$ 61 <sup>b</sup>     | 186.7 $\pm$ 67.5 <sup>b</sup>  |
| Postprandial blood glucose (mg/dl) | 106.5 $\pm$ 10.1 <sup>a</sup>   | 304.4 $\pm$ 91.9 <sup>b</sup>   | 281 $\pm$ 116 <sup>b</sup>     |
| HbA1C (%)                          | 4.87 $\pm$ 0.3 <sup>a</sup>     | 10.15 $\pm$ 2.63 <sup>b</sup>   | 8.44 $\pm$ 1.29 <sup>c</sup>   |
| Urea (mg/dl)                       | 20.5 $\pm$ 4.8 <sup>a</sup>     | 29.3 $\pm$ 10 <sup>a</sup>      | 93.6 $\pm$ 43.5 <sup>b</sup>   |
| Creatinine (mg/dl)                 | 0.7 $\pm$ 0.1 <sup>a</sup>      | 0.8 $\pm$ 0.12 <sup>a</sup>     | 5.2 $\pm$ 3.2 <sup>b</sup>     |
| eGFR (ml/min/1.73 m <sup>2</sup> ) | 116.46 $\pm$ 13.66 <sup>a</sup> | 107.66 $\pm$ 15.53 <sup>a</sup> | 18.53 $\pm$ 17.43 <sup>b</sup> |
| Adropin (ng/ml)                    | 0.853 $\pm$ 0.166 <sup>a</sup>  | 0.697 $\pm$ 0.155 <sup>b</sup>  | 0.648 $\pm$ 0.156 <sup>c</sup> |

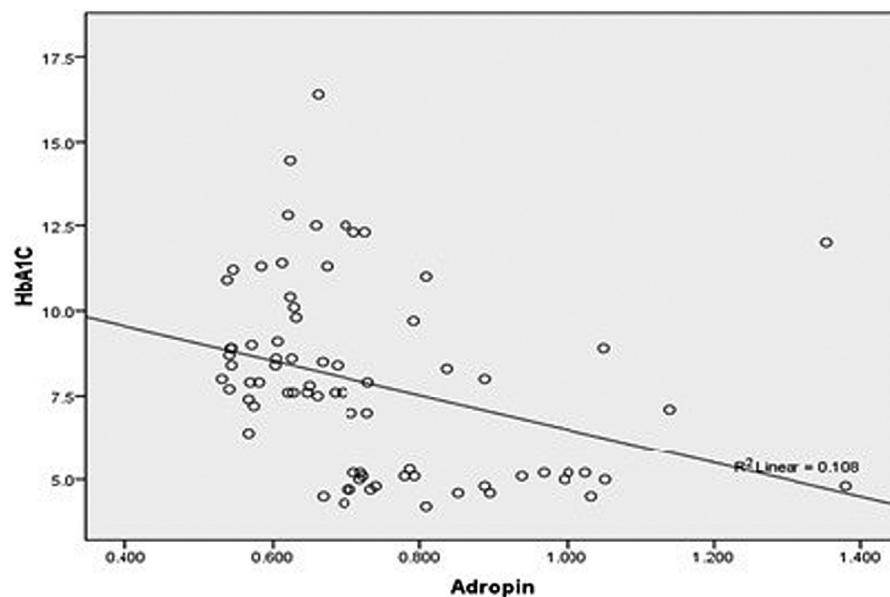
Data are represented as mean $\pm$ SD. DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; HbA1C, glyated hemoglobin; T2DM, type 2 diabetes mellitus. All different letters (a, b, c) in same row are significant at  $P$  value less than or equal to 0.05, using analysis of variance or  $\chi^2$  tests.

Figure 1



Correlation between serum adropin level and T2DM duration. T2DM, type 2 diabetes mellitus.

Figure 2



Correlation between serum adropin level and HbA1C value. HbA1C, glycated hemoglobin.

Sensitivity and specificity of adropin in T2DM were 50 and 100%, respectively, at a cutoff value less than or equal to 0.667 ng/ml. Adropin can be a significant predictor of T2DM when compared with normal participants, with the positive predictive value at this cutoff limit is 100% and the negative predictive value is 85.7% (Fig. 4).

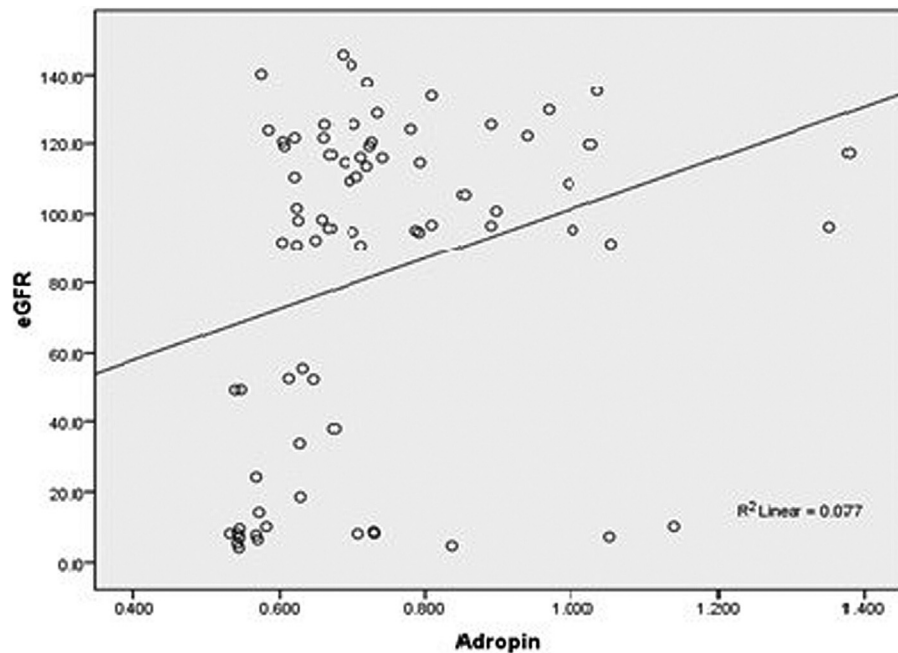
Sensitivity and specificity of adropin in DN were 40 and 100% at a cutoff value less than or equal to

0.571 ng/ml. The positive predictive value at this cutoff limit is 100% and the negative predictive value is 71.4%. *P* value more than 0.05 presents the differentiating ability of adropin between T2DM and DN insignificant (Fig. 5).

### Discussion

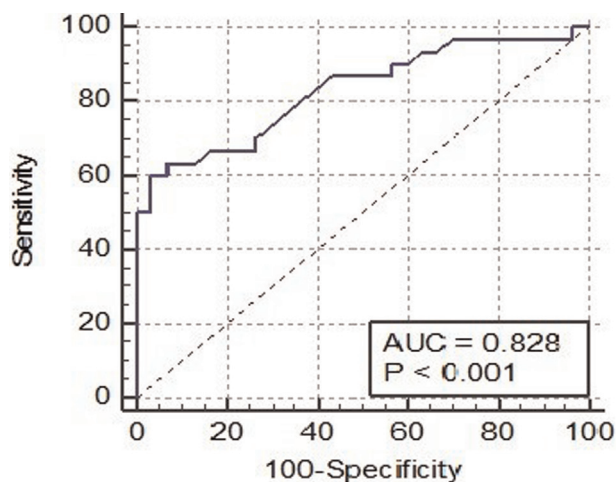
In this study, serum adropin level was lower in diabetic patients without nephropathy when compared with

Figure 3



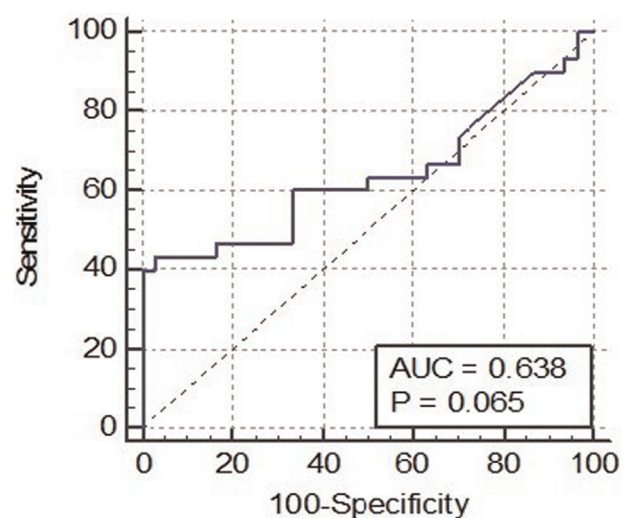
Correlation between serum adropin level and eGFR value. eGFR, estimated glomerular filtration rate.

Figure 4



Adropin sensitivity and specificity in patients with T2DM. T2DM, type 2 diabetes mellitus.

Figure 5



Adropin sensitivity and specificity in diabetic nephropathy (DN) group.

the control group, and this is in agreement with Wu *et al.* [13]. Moreover, this finding is consistent with Yosae *et al.* [14], who found low levels of adropin in T2DM, and this was correlated with metabolic syndrome. Therefore, these investigators identify adropin as a potentially protective agent against metabolic syndrome development. Metabolic syndrome is considered a prediabetes stage, and persons with this syndrome are at great risk of developing frank T2DM. Adropin is a protective agent against metabolic syndrome, and this may explain why persons with T2DM have lower levels of

adropin. Because they have low levels of adropin, they are easily affected by T2DM [14]. This result is also consistent with Zang *et al.* [15], who reported that serum adropin concentrations are decreased in patients with T2DM, especially those who are overweight/obese. Adropin maintains glucolipid homeostasis and insulin sensitivity, and its deficiency may be implicated in the pathogenesis of T2DM [15]. Similar result was reported by Li *et al.* [16], Li *et al.* [17], and Jasaszewili *et al.* [18] whose studies exhibited a significant remarkable decline of adropin in diabetic patients than those without diabetes.

In a study by Chen *et al.* [19] Enho gene mutations (the gene encoding for adropin) were found in three generations of a family with the common feature of T2DM. The investigators evaluated serum adropin level and regulatory T lymphocytes in these generations and found that both serum adropin level and regulatory T lymphocytes are significantly decreased in these family members with T2DM when compared with healthy participants. Moreover, the investigators found similar results in adropin knockout mice. They reported a significant correlation between adropin deficiency and regulatory T-cell deficiency [19]. Visceral adipose tissue invasion by proinflammatory macrophages is considered a key event driving adipose tissue inflammation and insulin resistance. Adropin enhances Tregs (regulatory T lymphocytes), which are involved in controlling the inflammatory state of adipose tissue, and thus enhancing insulin sensitivity. Therefore, adropin deficiency may play a role in the pathogenesis of T2DM [19,20].

The result of this study is also in agreement with Jurrisen *et al.* [21], adropin deficiency limits glucose uptake by skeletal muscles, and this contributes to impaired glucose tolerance and development of T2DM. Vascular insulin resistance is a hallmark of T2DM, and blunting of insulin-induced dilation is its primary manifestation. Importantly, in T2DM, reduced insulin-induced dilation and blood flow to skeletal muscle significantly limits glucose uptake and contributes to impaired glucose homeostasis. Adropin deficiency contributes to vascular insulin resistance, and treatment with adropin significantly improves insulin-induced dilation and glucose uptake by skeletal muscles [21].

In the present study, serum adropin level showed significant reduction in patients with DN versus patients with T2DM without DN. Hu and Chen [22] reported that patients with T2DM display decreased serum adropin concentrations compared with healthy controls. Their study showed that decreased serum adropin concentrations are also correlated with the development and progression of DN. The precise role of adropin in DN mechanism remains unclear. Inflammation plays an important role in the development of DN. Circulating adropin level is negatively correlated with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6) levels. Therefore, adropin may play a protective role in DN development through anti-inflammatory effects, and its deficiency may be implicated in the pathogenesis of DN [22].

Shelest and Buriakovska [23] concluded that adropin statistically decreased in the patients with DN. There

are many factors involved in the pathogenesis of DN, but among basic are endothelial and inflammatory ones [23]. Chronically activated immune system and persistent low-grade inflammation in diabetes have been proposed as a contributor to DN. Inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, and IL-8 are much more expressed in renal tissue of diabetics. These cytokines correlate positively with the degree of albuminuria in diabetic patients. Moreover, they contribute to glomerular basement membrane thickening, increase in endothelial permeability, apoptosis, and they have direct toxic effect on renal cells [24]. Adropin is suggested as an important player in DN development as its deficiency is associated with elevated levels of TNF- $\alpha$ , IL-1, IL-6, and highly sensitive C-reactive protein [23]. Adropin enhances endothelial form of nitric oxide synthase, modulates nitric oxide bioavailability, and thus, exerts an endothelial protection. Adropin deficiency is associated with elevated levels of vasoconstriction factor endothelin-1. The disturbance in these two vasoactive substances associating adropin deficiency may be implicated in the pathogenesis of DN [24,25].

Adropin might open new therapeutic opportunities in DN, as it targets many underlying mechanisms involved in the pathogenesis of DN, including insulin resistance, inflammation, and vascular disturbances [22]. Moreover, it can be possibly used in DN diagnosis; however, this is not specific, as its level is reduced in many other conditions including ischemic strokes, coronary artery diseases, inflammatory bowel diseases, nonalcoholic fatty liver disease, and polycystic ovary disease [21].

---

## Conclusion

Serum level of adropin was significantly lower in patients with DN than in patients with T2DM, which have a significantly lower adropin levels than in nondiabetics. Adropin could be used as a significant predictor of T2DM; however, it should be considered that its level is affected in many other diseases, reducing its diagnostic potentialities. Further work is needed to confirm and outline the role of adropin in T2DM and DN, particularly at the molecular levels. Attempts to use adropin in treating T2DM or protecting from its complications are still under experimental trails, and further research studies are needed to outline its possible therapeutic potentials.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- 1 American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care* 2017; 40; Suppl 1:1- S24.
- 2 Petersmann A, Nauck M, Muller-Wieland D, Kerner W, Muller UA, Landgraf R, *et al.* Definition, classification and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diab* 2018; 126:406–410.
- 3 Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, *et al.* Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013; 24:302–308.
- 4 Sato K, Yamashita T, Shirai R, Shibata K, Okano T, Yamaguchi M, *et al.* Adropin contributes to anti-atherosclerosis by suppressing monocyte-endothelial cell adhesion and smooth muscle cell proliferation. *Int J Mol Sci* 2018; 19:1293.
- 5 Kutlu O, Altun O, Dikler O, Aktas S, Ozsoy N, Arman Y, *et al.* Serum adropin levels are reduced in adult patients with nonalcoholic fatty liver disease. *Med Princ Pract* 2019; 28:463–469.
- 6 Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: diagnosis and treatment. *Nat Rev Endocrinol* 2013; 9:713–723.
- 7 Koetje PM, Spaan JJ, Kooman JP, Spaanderman ME, Peeters LL. Pregnancy reduces the accuracy of the estimated glomerular filtration rate based on Cockcroft-Gault and MDRD formulas. *Reprod Sci* 2011; 18:456–462.
- 8 Braham D, Trinder P. Estimation of glucose by glucose oxidase method. *J Analyst* 1972; 97:142–145.
- 9 Zander R, Lang W, Wolf HU. Alkaline haematin D-575, a new tool for the determination of hemoglobin as an alternative to the cyanhaemoglobin method, I Description of the method. *Clin Chem Act J* 1984; 136:83–93.
- 10 Gutmann I, Bergmeyer HU. Urea. *Methods of enzymatic analysis*. 2nd ed. H. U. Bergmeyer: Academic Press; 1974. 1791–1801.
- 11 Fossati P, Prencipe L, Berti G. Enzymic creatinine assay: a new colorimetric method based on hydrogen peroxide measurement. *Clin Chem* 1983; 29:1494–1496.
- 12 Levesque R. SPSS programming and data management: a guide for SPSS and SAS users. Chicago: SPSS Inc; 2007.
- 13 Wu L, Fang J, Chen L, Zhao Z, Luo Y, Lin C, Fan L. Low serum adropin is associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. *Clin Chem Lab Med* 2014; 52:751–758.
- 14 Yosae S, Khodadost M, Esteghamati A, Speakman JR, Shidfar F, Nazarie MN, *et al.* Metabolic syndrome patients have lower levels of adropin when compared with healthy overweight/obese and lean subjects. *Am J Mens Health* 2017; 11:426–434.
- 15 Zang H, Jiang F, Cheng X, Xu H, X. Hu X. Serum adropin levels are decreased in Chinese type 2 diabetic patients and negatively correlated with body mass index. *Endocr J* 2018 65:685–691.
- 16 Li S, Sun J, Hu W, Liu Y, Lin D, Duan H, Liu F. The association of serum and vitreous adropin concentrations with diabetic retinopathy. *Ann Clin Biochem* 2019; 56:253–258.
- 17 Li B, Tian X, Guo S, Zhang M, Li J, Zhai N, *et al.* Pentraxin-3 and adropin as inflammatory markers of early renal damage in type 2 diabetes patients. *Int Urol Nephrol* 2020; 52:2145–2152.
- 18 Jaszszwili M, Billert M, Strowski MZ, Nowak KW, Skrzypski M. Adropin as a fat-burning hormone with multiple functions-review of a decade of research. *Molecules* 2020; 25:549.
- 19 Chen S, Zeng K, Liu QC, Guo Z, Zhang S, Chen XR, *et al.* Adropin deficiency worsens HFD-induced metabolic defects. *Cell Death Dis* 2017; 8:3008.
- 20 Brnic D, Martinovic D, Zivkovic PM, Tokic D, Hadjina IT, Rusic D, *et al.* Serum adropin levels are reduced in patients with inflammatory bowel diseases. *Sci Rep* 2020; 10:9264.
- 21 Jurrissen TJ, Fujie SJ, Ghiarone T, Ramirez-Perez FI, Lemitsu M, Maeda S, *et al.* Exposure to adropin improves insulin-induced dilation in arteries from type 2 diabetic mice. *FASEB J* 2020; 34:suppl 1:1.
- 22 Hu W, Chen L. Association of serum adropin concentrations with diabetic nephropathy. *Mediators Inflamm* 2016; 2016:6038261.
- 23 Shelest B, Buriakovska O. Adropin influence on nephropathy development in hypertensive patients associated with diabetes mellitus 2 type. *Atherosclerosis* 2019; 287:123–124.
- 24 Toth-Manikowski S, Atta MG. Diabetic kidney disease: pathophysiology and therapeutic targets. *J Diabetes Res* 2015; 2015:697010.
- 25 Han W, Zhang C, Wang H, Yang M, Guo Y, Li G, *et al.* Alterations of irisin, adropin, preptin and BDNF concentrations in coronary heart disease patients comorbid with depression. *Ann Transl Med* 2019; 7:298.