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Serum Adiponectin Related to Neovascularization Process in Diabetic Retinopathy

Mehtap Gökçe Margunato[1], Hale Aral[2], Özen Ayrancı Osmanbaşoğlu[3], Hülya Güngel[3], Esma Altunoğlu[4], Murat Usta[5], Şennur Köse[4], Erdinç Serin[6], Savaş Karataş[4]

[1]Çorlu State Hospital, Clinic of Medical Biochemistry, Tekirdağ, Turkey
[2]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Medical Biochemistry, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey
[4]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
[5]Giresun University Faculty of Medicine, Department of Medical Biochemistry, Giresun, Turkey
[6]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Medical Biochemistry, İstanbul, Turkey

ABSTRACT

Introduction: There's are similar mechanisms in the development of diabetic retinopathy (DR) and diabetic nephropathy (DN) in terms of inflammation and oxidative stress. We wanted to measure serum adiponectin (ADPN) levels in DR, considering the other clinical/laboratory findings in subgroups with or without DN.

Methods: A total of 122 patients were included; group 1 (non-diabetic, healthy subjects), group 2 (diabetic without DR, with/without albuminuria/proteinuria), group 3 (mild to moderate DR, without albuminuria/proteinuria) and group 4 (severe non-proliferative or proliferative DR, with albuminuria/proteinuria). DR grades were defined by the same ophthalmologist based on the clinical examination and angiographic findings.

Results: In diabetics, mean hemoglobin A1c was over 8.0%. Estimated glomerular filtration rate values and serum albumin levels were significantly lower in group 4 compared to group 1. Not ADPN/C-reactive protein (CRP) levels, but ADPN, ADPN/waist circumference, ADPN/body mass index and ADPN/fibrinogen were all significantly higher in group 4 compared to group 2. ADPN/CRP was positively correlated with high-density cholesterol in group 1, 2, 4, negatively correlated with triglyceride in group 3, 4, and positively correlated with hypertension in group 4.

Conclusion: We had increased serum ADPN and indices in the DR neovascularization process among diabetics. But, further loss of kidney function itself prevented the increase in serum ADPN/CRP levels. To estimate progression in the advanced stages of DR, serum ADPN/CRP was a valuable follow-up marker in DR, if there was no urinary loss of ADPN.

Keywords: Adiponectin, inflammation, diabetic complications, neovascularization, diabetic retinopathy

Introduction

Diabetic retinopathy (DR), seen in approximately 80% of patients with 10 or more years of type 2 diabetes mellitus (T2DM), is a major microvascular complication. Possibly, it is responsible for a large proportion of vision problems and blindness in the population (1). In addition to the duration of diabetes, DR development is strongly linked with chronic hyperglycemia; dyslipidemia, diabetic nephropathy (DN), hypertension and mitochondrial dysfunction accompanied by induced oxidative stress and is associated with abnormal adiponectin (ADPN) levels (1,2). Mitochondrial dysfunction is also associated with renal tubular epithelial cell injury and the occurrence of DN, and ADPN is involved in promoting mitochondrial biogenesis and functional renal tubular epithelial cells (3). The mechanisms in the development of DR and DN seem very similar in terms of inflammation and oxidative stress.

ADPN secreted by adipocytes exists as a trimer and three multimer forms: low molecular weight, medium molecular weight, high molecular weight (HMW). It has effects such as antidiabetic, anti-inflammatory, regulating endothelial functions, antioxidant, antiapoptotic, antiatherogenic, antithrombotic, inhibiting smooth muscle proliferation and facilitating vasodilation (4). In studies conducted in different ethnic groups, plasma ADPN levels were found to be low in patients with obesity and T2DM. In contrast, the degree of hypoadiponectinemia was closely related to the degree of insulin resistance and hyperinsulinemia rather than the degree of adiposity (5). There was a relation between CRP, ADPN and quantitative insulin resistance check index to detect microvascular

Address for Correspondence: Hale Aral MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Medical Biochemistry, İstanbul, Turkey
Phone: +90 532 220 01 50 **E-mail:** drhalearal@yahoo.com **ORCID ID:** orcid.org/0000-0003-1996-956X

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measurements [capillary density, urine albumin creatinine ratio (UACR) and endothelial measurements] in non-diabetic and normotensive healthy subjects (6).

The development of DR or albuminuria/proteinuria is accepted as findings in favor of endothelial dysfunction in the organism. The impact of UACR and estimated glomerular filtration rate (eGFR) on serum ADPN is clearly observed. As is known, the risk of cardiovascular disease (CVD) increases with endothelial dysfunction. As a result, ADPN has a positive effect on cardiovascular health. Its protective role against atherosclerosis is mediated by inhibiting vascular smooth muscle and endothelial cell proliferation. ADPN has been shown to be a good marker for metabolic control and atherosclerotic risk (7).

In this study, we investigated the relationship between serum ADPN or related indices and DR degree with or without albuminuria/proteinuria. Demographic/clinical/anthropometric findings, smoking status, blood pressure values, inflammatory blood markers and other routine laboratory findings were also considered.

Methods

A total of 122 patients, followed up in out-patient clinics of ophthalmology and internal medicine, were included our study. Patients with known thyroid dysfunction, urinary infection, nephropathy (of the non-diabetic causes), malignancy, diabetic neuropathy or eGFR <30 mL/min were all excluded. An approval of the research protocol was received by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 117, date: 08.04.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki) was received.

All the cases were divided into four different groups; group 1 (non-diabetics, n=27), group 2 (T2DM without retinopathy, with/without albuminuria and/or proteinuria n=45), group 3 (mild to moderate DR, without any albuminuria or proteinuria, n=26) and group 4 (severe non-proliferative or proliferative retinopathy, with albuminuria and/or proteinuria n=24). DR grades were defined by the same ophthalmologist based on clinical examination and angiographic findings.

Serum ADPN was run via immunoturbidimetric method (catalog no: AO 2999, Randox Laboratories Limited, Crumlin, UK) using AU2700 (Beckman Coulter Inc, Brea, Ca, USA). We found a coefficient of variation (within-run precision) of 1.45% at a serum level of 5.85 µg/mL (n=17), and 1.00% at a serum level of 12.05 µg/mL (n=19).

Anthropometric measurements of waist circumference (WC), height, weight and blood pressure were recorded. Data from the patient records were retrieved, the measurements were performed as follows; chemistry/immunochemistry assays using AU 2700 and Image 800 (Beckman Coulter Inc.), fibrinogen levels using BCS XP coagulometer (Siemens Healthcare Diagnostics Inc.), hemoglobin A1c (HbA1c) using (ADAMS HA-8180V (Arkray Inc.) and complete blood counts using BC 6800 (Mindray Medical International Ltd.). Spot urinalysis and some definitions were used as albuminuria (albumin/creatinine: ≥30 mg/g) and proteinuria (protein/creatinine >0.2 g/g).

Low-density-lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation. In eGFR values were estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation by Levey et al. (8); as follows, $eGFR_{CKD-EPI}$=141 x minimum (Scr/k,1)$^{\alpha}$ x maximum (Scr/k, 1)$^{-1.209}$ x0.993Age x 1.018 [if female].

Indices of ADPN were estimated as ADPN/BMI, ADPN/WC, ADPN/fibrinogen, ADPN/CRP.

Statistical Analysis

We used MedCalc (MedCalc Software, Broekstraat, Mariakerke, Belgium). The Kolmogorov-Smirnov tests investigated Gaussian distribution. Non-gaussian variables were given as median (25th percentile-75th percentile), or else mean ± standard deviation. In comparison, One-Way ANOVA or Kruskal-Wallis H test was used in multiple group comparisons. Tukey HSD and Tamhane's T^2 test for One-Way ANOVA, or Mann-Whitney U test for Kruskal-Wallis H test were used in post hoc comparisons. Pearson's chi-square test, Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (rs) was used. All statistical tests were two-sided, and p-values less than 0.05 were considered to indicate significance, except p values less than 0.008 when the Mann-Whitney U test was used for post-hoc test.

Results

No significant difference in the male-to-female ratio was found among all the groups (groups 1-4), as shown in Table 1. Also, no statistically significant difference was found among the age, body mass index (BMI), and WC among the diabetics (groups 2-4).

Each diabetic-subgroup presented a mean of HbA1c over 8.0% and dyslipidemia with high triglyceride levels, as shown in Table 2. Also, diabetics had significantly decreased iron, hemoglobin levels and increased white blood cell values. CRP was higher in group 2, 3 than the controls. Serum urea and creatinine were higher in group 4 compared to group 1. However, eGFR values and serum albumin levels decreased in group 4 compared with group 1.

Table 1. Demographic data, anthropometric measurements and smoking status of controls and diabetic sub-groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Age (years)	49.7±10.1	58.0±11.1[a]	62.2±6.5[b]	62.2±8.9[b]	**<0.0001**
Male/female (N/N)	11/16	19/26	15/11	10/14	=0.5440
Body mass index (kg/m^2)	25.5±4.3	31.9±6.1[b]	31.9±4.4[b]	32.2±5.5[b]	**<0.0001**
Waist circumference (cm)	89.8±15.5	105.4±11.1[b]	103.6±23.5[a]	108.3±10.6[b]	**<0.0001**
Smoking (%)	22.2%	42.2%	50.0%	29.2%	=0.2990

[a]Tukey test, p<0.01 vs. group 1, [b]Tukey test, p<0.0001 vs. group 1

In healthy subjects (group 1), we had higher ADPN/CRP median values compared to group 2 and group 3 (Table 3). However, ADPN, ADPN/WC, ADPN/BMI and ADPN/fibrinogen were higher in group 4, compared with group 2, except ADPN/CRP.

ADPN/CRP was correlated with high-density cholesterol (HDL-C) in group 1, 2, 4 (Table 4). There was a negative correlation between ADPN/CRP and triglycerides in group 3, 4. In group 4, ADPN/CRP was also correlated with hypertension.

Discussion

The results demonstrated in this work provide a new perspective on understanding ADPN pathophysiology in different grades of DR. ADPN/CRP was significantly decreased in group 2, 3 (in diabetics), according to the healthy subjects. Theoretically, the terminal stage of various chronic diseases can occur in different ways in humans and experimental models; the ADPN paradox is alive among them. One possibility is that the persistence of the terminal stage of chronic diseases for which medical care is sought in humans contributes to the loss of ADPN function and may be related to metabolic syndrome (9). Although a significant negative correlation was shown between serum ADPN levels and smoking in women by Persson et al. (10), we had no difference in smoking percentage among all the groups in our study.

ADPN and indices of ADPN/BMI, ADPN/WC, ADPN/fibrinogen values significantly increased in group 4, in which microvascular complications increased mostly (both DR ad DN), compared with group 2. We also showed that UACR and eGFR values had a significant effect on serum ADPN levels. ADPN levels increasing with DR degree may be associated with its anti-inflammatory protective effect. ADPN/CRP indices did not differ significantly, although there was no any increase in CRP levels decreasing ADPN/CRP ratio in group 4, compared with group 2. There was a negative correlation between ADPN/CRP and triglycerides in patients with DR, group 3, 4. Also, ADPN/CRP was correlated with hypertension as a macrovascular complication in group 4. The prominence of the ADPN/CRP index highlights the importance of both inflammation and neovascularization. ADPN influences endothelial adhesion and transmigration of leukocytes and macrophages (11).

Both positive and inverse associations between ADPN and DR progression have been reported in meta-analysis studies that combined various ethnic groups (1). ADPN plays a critical role in retinal oedema and neovascularization, and it's a potential therapeutic target for treating diabetic macular oedema, proliferative DR, and retinal vein occlusion (12) or DN (13); in an observational study, Kuo et al. (14) showed that ADPN levels increased with DR, and ADPN was seen positively correlated with DR progression.

Table 2. Routine laboratory data of controls and diabetic sub-groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Glucose (mg/dL)	94±9	175±64[d]	181±77[d]	161±58[d]	**<0.0001**
Hemoglobin A1c (%)	5.4±0.3	8.4±2.2[d]	8.9±2.1[d]	8.3±1.7[d]	**<0.0001**
Urea (mg/dL)	31±7	41±19[c]	39±16	49±17[d]	**<0.0010**
Creatinine (mg/dL)	0.77±0.22	0.99±0.41	0.94±0.49	1.10±0.49[a]	**=0.0330**
$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	95.1±16.8	78.7±27.6[a]	83.9±23.2	67.9±21.2[c]	**<0.0010**
Total cholesterol (mg/dL)	212±58	199±65	207±42	209±72	=0.8220
Triglyceride (mg/dL)	93 (64–108)	161 (121-198)[ε]	160 (93-204)[ε]	140 (106-219)[ε]	**<0.0001**
High-density lipoprotein cholesterol (mg/dL)	56±12	44±9[d]	45±7[c]	46±12[c]	**<0.0001**
Low-density lipoprotein cholesterol (mg/dL)	145±43	118±41	132±36	135±48	=0.0740
Total protein (g/dL)	7.3±0.5	7.4±0.5	7.5±0.4	7.2±0.4	=0.3010
Albumin (g/dL)	4.4±0.3	4.3±0.3	4.3±0.3	4.1±0.3[b]	**=0.0040**
Alanine aminotransferase (U/L)	18 (14-33)	20 (16-27)	21 (17-26)	19 (12-24)	=0.3550
Gamma-glutamyl transferase (U/L)	17 (14-23)	26 (19-37)[β]	20 (17-29)	21 (14-30)	**=0.0200**
Iron (µg/dL)	101 (74-132)	70 (46-97)[δ]	66 (50-83)[ε]	65 (53-99)[γ]	**<0.0010**
Total iron binding cap. (µg/dL)	326 (311-365)	369 (307-398)	364 (328-381)	349 (315-384)	=0.2470
Ferritin (ng/mL)	60 (27-96)	34 (11-82)	30 (10-56)	30 (15-52)	=0.0670
C-reactive protein (mg/dL)	0.24 (0.17-0.43)	0.48 (0.32-0.81)[ε]	0.47 (0.31-0.67)[α]	0.34 (0.15-0.88)	=0.0030
Fibrinogen (mg/dL)	342±70	379±91	364±63	396±91	=0.1170
Hemoglobin (g/dL)	14.4±1.1	13.5±2.0	13.1±2.3[e]	11.6±2.6[d,f]	**<0.0001**
Hematocrit (%)	44±3	42±6	42±5	39±5[c]	**=0.0060**
Thrombocyte (x10^3/µL)	220±43	277±75[c]	261±56[a]	249±91	**=0.0090**
White blood cell (x10^3/µL)	5.9±1.0	7.6±2.0[d]	7.7±2.2[d]	7.3±1.7[a]	**<0.0010**

[a]Tamhane's T^2 or Tukey test, p<0.05 vs. group 1, [b]Tamhane's T^2 or Tukey test, p<0.01 vs. group 1, [c]Tamhane's T^2 or Tukey test, p<0.001 vs. group 1, [d]Tamhane's T^2 or Tukey test, p<0.0001 vs. group 1, [e]Tamhane's T^2 or Tukey test, p<0.01 vs. group 2, [f]Tamhane's T^2 or Tukey test, p<0.05 vs. group 3, [α]Mann-Whitney U test, p=0.002 vs. group 1, [β]Mann-Whitney U test, p=0.003 vs. group 1, [γ]Mann-Whitney U test, p=0.006 vs. group 1, [δ]Mann-Whitney U test, p<0.001 vs. group 1, [ε]Mann-Whitney U test, p<0.0001 vs. group 1, eGFR: Estimated glomerular filtration rate

In diabetic animal models, ADPN was upregulated in damaged muscle tissue (15), and it was shown that after myocardial injury ADPN levels increase to be a part of the revascularization process (16). Therefore, it is possible in the DR neovascularization process to have increased ADPN levels.

In a cross-sectional study, there was an association between plasma ADNP level and the variance of ADPN related genes on the DR status, individually and in combination (17). Moreover, genes associated with CVD are the *ADPN* gene and apolipoprotein E polymorphism gene with the x2 allele (18).

In another study, serum ADPN levels decreased in DN, but higher levels were found in DR or diabetic neuropathy (19), these findings support our results. In a meta-analysis, ADPN levels were higher in T2DM patients with microvascular complications (20). Plasma ADPN levels increased significantly with the severity of DN; they were associated with eGFR and UACR. The relative risk of impaired renal function requiring dialysis was found to be independent of ADPN levels (21). Additionally, a cohort study showed that ADPN levels were significantly increased in patients with chronic kidney disease (22), however when we consider that clearance of ADPN is mainly processed in the liver, renal function loss itself doesn't contribute to ADPN elevation (23).

According to some studies, no correlation was found between ADPN and serum lipids in the form of triglycerides, LDL-C or total cholesterol (24,25). In another study, ADPN correlated positively with total cholesterol and HDL-C (21). In our study, ADPN/CRP was negatively correlated with triglycerides in group 3 and group 4. Additionally, there were varying degrees of positive correlations between ADPN/CRP and HDL-C levels in group 1, group 2, and group 4. Still a stronger correlation was found in non-diabetics, group 1. Patients with DR were included in groups 3 and 4; also, there was DR progression, especially in the proliferative phase in group 4. In group 4, a weak negative correlation was found between ADPN/CRP and hypertension. The fact that the parameters of eGFR or albumin in group 4 did not differ from the diabetic control group (group 2) strengthened our study to see the pure effect of the severity of DR progression, especially in the proliferative phase.

Blood levels of irisin, another adipokine, decreased with increasing stage of chronic kidney disease (UACR ≥300 mg/g, eGFR <60 mL/min 1.73 m^2) and insulin resistance. It was also significantly associated with sarcopenia and carotid atherosclerosis in patients receiving peritoneal dialysis (26).

Recently, increased HMW level or HMW/total ratio has been associated with visceral fat type obesity, diabetes, glucose tolerance and insulin resistance, CVD, metabolic syndrome. Urinary ADPN was shown to be useful as a surrogate marker for DN risk performed with ultra-sensitivity by employing a two-site immune complex transfer enzyme immunoassay fluorescently after gel filtration of immunoreactivity; urinary concentrations of HMW- ADPN (size, >250 kD) increased as the disorder progresses in the glomerular molecular barrier (27). Urinary ADPN levels were much better than that of UACR, as a reliable indicator of proteinuria (28). Also, it was suggested that the increase in urinary ADPN was associated with the decreased renal function (UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m^2) (29). Total and HMW-ADPN levels correlated moderate to highly with UACR and eGFR within a fully automated immunoassay system (30).

Study Limitations

The most important limitation was the number of patients and having no sub-groups at variable stages of diabetes. Moreover, it should be better to include diabetic neuropathy. For technical reasons, we could not reach the patient group with isolated or accompanying diabetic

Table 3. Comparison of uric acid and adiponectin findings of all the groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Uric acid (mg/dL)	5.0±1.2	6.0±1.4	5.6±1.5	5.6±1.2	**=0.0160**
Adiponectin (µg/mL)	8.4 (5.3-10.3)	6.5 (4.3-11.0)	6.6 (4.7-9.9)	11.6 (6.0-14.9)[d]	**=0.0280**
Adiponectin/body mass index (µg.m^2/kg.mL)	0.36 (0.21-0.49)	0.21 (0.13-0.34)	0.21 (0.15-0.30)	0.36 (0.21-0.43)[e]	**=0.0070**
Adiponectin/waist circumference (µg/cm.mL)	0.093 (0.058-0.138)	0.064 (0.039-0.099)	0.06 (0.05-0.102)	0.106 (0.056-0.134)[e]	**=0.0150**
Adiponectin/C-reactive protein (µg.dL/mg.mL)	34.2 (16.3-50.6)	15.4 (8.1-23.0)[a]	13.0 (8.3-23.7)[b]	21.3 (10.3-92.2)	**<0.0010**
Adiponectin/fibrinogen (µg.dL/mg.mL)	0.022 (0.016-0.032)	0.019 (0.011-0.025)	0.019 (0.015-0.024)	0.030 (0.018-0.042)[c]	**=0.0180**

[a]Mann-Whitney U test, p<0.0001 vs. group 1, [b]Mann-Whitney U test, p=0.003 vs. group 1, [c]Mann-Whitney U test, p=0.004 vs. group 2, [d]Mann-Whitney U test, p=0.005 vs. group 2, [e]Mann-Whitney U test, p=0.008 vs. group 2

Table 4. Lipid panel, and inflammatory parameters significantly correlated with ADPN/CRP, in the groups

Parameters	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)
Total cholesterol	N.S.	rs=0.381 (p=0.012)	r_s=-0.457 (p=0.019)	N.S.
Triglyceride	N.S.	N.S.	r_s=-0.540 (p=0.004)	r_s=-0.450 (p=0.027)
High-density lipoprotein cholesterol	r_s=0.520 (p=0.005)	r_s=0.387 (p=0.010)	N.S.	r_s=0.398 (p=0.054)
Low-density lipoprotein cholesterol	N.S.	r_s=0.365 (p=0.016)	r_s=-0.409 (p=0.038)	N.S.
White blood cell	N.S.	N.S.	r_s=-0.378 (p=0.057)	N.S.
Fibrinogen	N.S.	N.S.	N.S.	N.S.
Hypertension	N.S.	N.S.	N.S.	rrb=-0.362 (p=0.082)

ADPN: Adiponectin, CRP: C-reactive protein

neuropathy, another microvascular complication. The second limitation was that the control group was younger. And data including diabetic age was confidential.

Conclusion

We had increased serum ADPN and indices of ADPN/BMI, ADPN/WC, ADPN/fibrinogen values in the DR neovascularization process among diabetics, so clinicians can be encouraged to benefit from this immunoturbidimetric assay for diabetics via personalized medicine approach. But, further loss of kidney function itself prevented the increase in serum ADPN/CRP levels. To estimate progression in the advanced stages of DR, serum ADPN/CRP was a valuable marker, if there was no urinary loss of ADPN.

Meanwhile, more expanded studies should be performed where ADPN isoforms (molecular weight and immunoreactivity) or indices evaluated together with hepatic steatosis determined sonographically, and endothelial dysfunction or heart status determined radiologically for monitoring other vascular complications of diabetes. Besides biomarkers and imaging findings, life-style conditions, including exercise and dietary options/habits, should be recorded.

Ethics Committee Approval: An approval of the research protocol by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 117, date: 08.04.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki) was received.

Informed Consent: It wasn't obtained.

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References

1. Huang YC, Chang YW, Cheng CW, Wu CM, Liao WL, Tsai FJ. Causal relationship between adiponectin and diabetic retinopathy: A Mendelian randomization study in an Asian population. Genes (Basel) 2020; 12: 17.
2. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis 1998; 31: 947-53.
3. Chen Y, Yang Y, Liu Z, He L. Adiponectin promotes repair of renal tubular epithelial cells by regulating mitochondrial biogenesis and function. Metabolism 2022; 128: 154959.
4. Ebrahimi-Mamaeghani M, Mohammadi S, Arefhosseini SR, Fallah P, Bazi Z. Adiponectin as a potential biomarker of vascular disease. Vasc Health Risk Manag 2015; 11: 55-70.
5. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930-5.
6. Cheng C, Daskalakis C. Association of adipokines with insulin resistance, microvascular dysfunction, and endothelial dysfunction in healthy young adults. Mediators Inflamm 2015; 2015: 594039.
7. Bråkenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A 2004; 101: 2476-81.
8. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000; 11: 155A.
9. Karamian M, Moossavi M, Hemmati M. From diabetes to renal aging: the therapeutic potential of adiponectin. J Physiol Biochem 2021; 77: 205-14.
10. Persson J, Strawbridge RJ, McLeod O, Gertow K, Silveira A, Baldassarre D, et al. Sex-specific effects of adiponectin on carotid intima-media thickness and incident cardiovascular disease. J Am Heart Assoc 2015; 4: e001853.
11. Kacso T, Bondor CI, Rusu CC, Moldovan D, Trinescu D, Coman LA, et al. Adiponectin is related to markers of endothelial dysfunction and neoangiogenesis in diabetic patients. Int Urol Nephrol 2018; 50: 1661-6.
12. Nishinaka A, Nakamura S, Tanaka M, Masuda T, Inoue Y, Yamamoto T, et al. Excess adiponectin in eyes with progressive ocular vascular diseases. FASEB J 2021; 35: e21313.
13. Lee JY, Yang JW, Han BG, Choi SO, Kim JS. Adiponectin for the treatment of diabetic nephropathy. Korean J Intern Med 2019; 34: 480-91.
14. Kuo JZ, Guo X, Klein R, Klein BE, Genter P, Roll K, et al. Adiponectin, insulin sensitivity and diabetic retinopathy in latinos with type 2 diabetes. J Clin Endocrinol Metab 2015; 100: 3348-55.
15. Delaigle AM, Senou M, Guiot Y, Many MC, Brichard SM. Induction of adiponectin in skeletal muscle of type 2 diabetic mice: in vivo and in vitro studies. Diabetologia 2006; 49: 1311-23.
16. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin Chim Acta 2007; 380: 24-30.
17. Liao WL, Chen YH, Chen CC, Huang YC, Lin HJ, Chen YT, et al. Effect of adiponectin level and genetic variation of its receptors on diabetic retinopathy: A case-control study. Medicine (Baltimore) 2019; 98: e14878.
18. Wong YH, Wong SH, Wong XT, Yap QY, Yip KY, Wong LZ, et al. Genetic associated complications of type 2 diabetes mellitus: a review. Panminerva Med 2021; 64: 274-88.
19. Jung CH, Kim BY, Mok JO, Kang SK, Kim CH. Association between serum adipocytokine levels and microangiopathies in patients with type 2 diabetes mellitus. J Diabetes Investig 2014; 5: 333-9.
20. Rodríguez AJ, Nunes Vdos S, Mastronardi CA, Neeman T, Paz-Filho GJ. Association between circulating adipocytokine concentrations and microvascular complications in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of controlled cross-sectional studies. J Diabetes Complications 2016; 30: 357-67.
21. Cha JJ, Min HS, Kim K, Lee MJ, Lee MH, Kim JE, et al. Long-term study of the association of adipokines and glucose variability with diabetic complications. Korean J Intern Med 2018; 33: 367-82.
22. Fumeron F, El Boustany R, Bastard JP, Fellahi S, Balkau B, Marre M, et al. Plasma total adiponectin and changes in renal function in a cohort from the community: the prospective Data from an Epidemiological Study on the Insulin Resistance Syndrome study. Nephrol Dial Transplant 2021; 36: 2058-65.
23. Halberg N, Schraw TD, Wang ZV, Kim JY, Yi J, Hamilton MP, et al. Systemic fate of the adipocyte-derived factor adiponectin. Diabetes 2009; 58: 1961-70.

24. Fujita H, Morii T, Koshimura J, Ishikawa M, Kato M, Miura T, et al. Possible relationship between adiponectin and renal tubular injury in diabetic nephropathy. Endocr J 2006; 53: 745-52.

25. Alnaggar ARLR, Sayed M, El-Deena KE, Gomaa M, Hamed Y. Evaluation of serum adiponectin levels in diabetic nephropathy. Diabetes Metab Syndr 2019; 13: 128-31.

26. Wang R, Liu H. Association between serum irisin and diabetic nephropathy in patients with type 2 diabetes mellitus: A meta-analysis. Horm Metab Res 2021; 53: 293-300.

27. Yamamoto M, Fujimoto Y, Hayashi S, Hashida S. A study of high-, middle- and low-molecular weight adiponectin in urine as a surrogate marker for early diabetic nephropathy using ultrasensitive immune complex transfer enzyme immunoassay. Ann Clin Biochem 2018; 55: 525-34.

28. Yamakado S, Cho H, Inada M, Morikawa M, Jiang YH, Saito K, et al. Urinary adiponectin as a new diagnostic index for chronic kidney disease due to diabetic nephropathy. BMJ Open Diabetes Res Care 2019; 7: e000661.

29. Ishizu M, Mori H, Ohishi M, Kuroda A, Akehi Y, Yoshida S, et al. Urinary adiponectin excretion is an early predictive marker of the decline of the renal function in patients with diabetes mellitus. J Diabetes Complications 2021; 35: 107848.

30. Watanabe T, Fujimoto Y, Morimoto A, Nishiyama M, Kawai A, Okada S, et al. Development of fully automated and ultrasensitive assays for urinary adiponectin and their application as novel biomarkers for diabetic kidney disease. Sci Rep 2020; 10: 15869.