The role of adiponectin in diabetic retinopathy and insulin resistance

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ABSTRACT

Diabetic retinopathy (DR) is a common microvascular complication of type 2 diabetes mellitus (T2DM). The pathogenesis of DR is multifactorial, involving chronic hyperglycemia, oxidative stress, inflammation, and insulin resistance (IR), all of which contribute to microvascular damage in the retina. This study aimed to evaluate the role of adiponectin (APN) in DR and its correlation with IR, inflammatory, and glycemic control. A total of 100 T2DM patients were enrolled and equally divided into two groups based on the presence or absence of DR. Demographic characteristics, glycemic indices, IR, inflammatory markers, and serum APN levels were analyzed. The diagnostic performance of APN was assessed using receiver operating characteristic (ROC) curve analysis. Patients with DR had a significantly longer duration of diabetes compared to those without DR ($p<0.001$). Biochemically, the DR group showed significantly higher levels of fasting blood sugar ($p=0.025$), hemoglobin A1C ($p=0.003$), fasting insulin ($p=0.005$), homeostatic model assessment for IR ($p=0.001$), and C-reactive protein ($p<0.001$). Conversely, the median serum APN levels were significantly lower in DR patients (median: 2.65 ng/mL) than in those without DR (median: 5.36 ng/mL; $p<0.001$). ROC analysis revealed that APN had a fair diagnostic performance for detecting DR (area under the curve: 0.773, 95% confidence interval: 0.679-0.867, $p<0.001$). DR is associated with poor glycemic control, increased IR, elevated inflammatory markers, and reduced serum APN levels. APN may serve as a potential biomarker for the detection and risk stratification of DR in T2DM patients.

Introduction

Diabetic retinopathy (DR) is among the most prevalent microvascular complications of diabetes, primarily driven by prolonged hyperglycemia. Chronic high blood glucose disrupts intracellular metabolic pathways, leads to pericyte loss, impairs retinal circulation, and results in ischemia and hypoxia, culminating in proliferative retinopathy.[1] Multiple risk factors contribute to the development of DR, including genetic susceptibility, duration of diabetes, lipid metabolism abnormalities, puberty, pregnancy, and hypertension.[2]

Adiponectin (APN), a hormone secreted mainly by adipose tissue, plays a central role in maintaining metabolic balance by regulating glucose levels and improving insulin sensitivity. It is a 244-amino acid polypeptide that circulates in various multimeric forms, with the high-molecular-weight complexes being the most biologically active in enhancing insulin sensitivity.[3] Unlike most adipokines, APN levels are inversely correlated with body fat, meaning that levels are

typically lower in individuals with obesity, a known risk factor for type 2 diabetes mellitus (T2DM).[4]

The effects of APN are mediated through its receptors, AdipoR1 and AdipoR2, which are widely distributed across tissues such as the liver and skeletal muscle. These receptors activate key metabolic pathways, including AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-α, which are essential for increasing fatty acid oxidation, glucose uptake, and decreasing hepatic gluconeogenesis.[5] For instance, AMPK activation inhibits acetyl-CoA carboxylase, reducing lipid accumulation in muscle and enhancing insulin signaling.[6] Additionally, APN exerts anti-inflammatory effects by downregulating cytokines like tumor necrosis factor (TNF)-α, further supporting insulin sensitivity.[7]

Low APN levels, referred to as hypoadiponectinemia, are characteristic of obesity-related insulin resistance (IR) and T2DM. Certain genetic variants in the *ADIPOQ* gene, such as SNPs rs2241766 and rs1501299, have been linked to reduced APN levels and increased diabetes risk.[8] Importantly, longitudinal studies suggest that lower APN levels can precede the clinical onset of T2DM, highlighting its potential predictive value.[9]

However, the relationship between APN and DR remains controversial. Several investigations, including those by Dossarps and Mao, found no significant association between serum APN and DR.[10,11] IR is a critical component of T2DM and the metabolic syndrome. APN shows an inverse association with both IR and adiposity. Proposed mechanisms of action include inhibition of gluconeogenesis, stimulation of fatty acid oxidation *via* AMPK activation, and reduction of hepatic ceramides through ceramidase activation.[12] The present study aimed to evaluate the role of APN in DR and its correlation with IR, inflammatory, and glycemic control.

Materials and Methods

This investigation constituted a prospective cross-sectional study encompassing a cohort of 100 outpatients diagnosed with T2DM, who were receiving care at the outpatient clinics of Al-Imamain Al-Kadhumain Medical City, Baghdad, over the timeframe extending from January 1, 2024, to January 1, 2025. The participants were classified into two distinct groups: group I consisted of patients with T2DM devoid of retinopathy (50 individuals). The diagnosis of type 2 diabetes was established based on a fasting blood glucose level ≤126 mg/dL or a hemoglobin A1c (HbA1c) value exceeding 6.5%. Conversely, group II comprised 50 diabetic patients exhibiting retinopathy. The diagnosis of DR was conducted in accordance with the International Clinical Diabetic Retinopathy Severity Scale, as endorsed by the American Academy of Ophthalmology and the International Council of Ophthalmology.[13]

Prior to the commencement of data collection, a written informed consent was procured from each participant following a comprehensive explanation of the study's objectives. The confidentiality of the data throughout the research was assured, and the participants were informed that the data would be utilized solely for research purposes. The study received approval from the Institutional Review Board of the College of Medicine at Al-Nahrain University (approval No. 124-2025).

Demographic information, including age, gender, weight, and height [from which body mass index (BMI) was derived], waist circumference (WC), past medical history (PMH), and the duration of T2DM, was acquired through direct interviews conducted with the patients.

Biochemical tests

Participants were instructed to abstain from all food and beverage intake for a duration of 8 hours before the collection of biological samples. On the subsequent morning, a total volume of 5 mL of venous blood was obtained from each participant. The blood specimens were divided into two aliquots, specifically 3 mL and 2 mL, respectively. For serum extraction, 3 mL of blood was deposited into a gel tube. Subsequently, serum was isolated by subjecting the sample to centrifugation for 15 minutes at a force of 4000×g. The resultant serum was collected and aliquoted into multiple Eppendorf tubes for subsequent biochemical and molecular analyses. The remaining 2 mL of blood was procured in ethylene diamine tetra-acetic acid tubes for hematological and molecular evaluations. Colorimetric techniques were employed to quantify fasting blood sugar (FBS) levels. Commercially available kits (Sunlong Biotech, China) were utilized to assess the serum concentrations of fasting insulin, C-reactive protein (CRP), and APN. A sandwich assay was established wherein a pre-coated antibody was positioned at the base, the CRP was situated in the middle, and an antibody conjugated to horseradish peroxidase was placed atop after the incubation period. Unbound components were subsequently removed through washing, and the bound peroxidase activity was evaluated *via* the substrate reaction. The reaction was then halted with sulfuric acid, and the optical density was measured using a standard microplate reader at a wavelength of 450 nm. The manufacturers' protocols were meticulously adhered to. The following equation was utilized to compute the Homeostatic Model Assessment-IR (HOMA-IR) 16: HOMA-IR = glucose (mg/dL) × insulin (mU/L)/405.

Statistical analysis

Statistical evaluations were conducted utilizing the SPSS software version 25.0 (IBM, Chicago, IL, USA). Continuous variables underwent normality testing (Shapiro-Wilk test); data exhibiting a normal distribution were expressed as mean and standard deviation, subsequently analyzed using the Student's *t*-test. Conversely, data that did not conform to a normal distribution were represented as median and range and analyzed *via* the Mann-Whitney U test. Categorical variables were delineated as counts and percentages and subjected to analysis using the Chi-square test. The receiver operating characteristic (ROC) curve was employed to assess the diagnostic capability of APN in the identification of DR. Spearman's correlation analysis was utilized to investigate potential correlations between APN and other variables. A p-value of less than 0.05 was deemed indicative of a statistically significant difference.

Results

Demographic characteristics of the patients

Although patients with DR had a higher mean age than those without retinopathy (55.16±7.97 *vs*. 52.38±8.85

years), the difference was not significant. Similarly, the two groups were comparable in terms of sex distribution, BMI, and WC, with no significant differences. However, patients with DR had longer disease duration (19.92±4.72 years) than those without retinopathy (8.64±3.15 years), with a highly significant difference (Table 1).

Clinical and biochemical characteristics of the patients

Table 2 compares clinical and biochemical parameters between diabetic patients with and without retinopathy. Except for PMH, all included clinical characteristics were significantly higher in patients with DR than in those without retinopathy. Patients with retinopathy had higher FBS levels (199.64±57.04 mg/dL) compared to those without (177.24±40.04 mg/dL; p=0.025), and higher HbA1c values (9.65±2.36% *vs*. 8.48±1.3%; p=0.003). Additionally, fasting insulin levels (19.35±4.71 µIU/mL *vs*. 14.35±4.71 µIU/mL; p=0.005) and HOMA-IR scores (9.22±5.59 *vs*. 6.29±2.61; p=0.001) were significantly elevated in patients with retinopathy. CRP levels were also markedly higher in the retinopathy group (4.75±3.4 mg/L) compared to the non-retinopathy group (2.19±1.36 mg/L; p<0.001).

Serum level of adiponectin

Data regarding the serum level of APN were found to be non-normally distributed. Accordingly, these data were expressed as median and range. The median serum levels of APN in diabetic patients without retinopathy were 5.36 ng/mL (range: 1.39-22.43 ng/mL), which was higher than that of diabetic patients with retinopathy (median: 2.65 ng/mL, range: 0.87-7.44) with a highly significant difference (Figure 1).

Table 1. Demographic characteristics of diabetic patients with and without retinopathy.

Variables	Without retinopathy (n=50)	With retinopathy (n=50)	p
Age, years			
Mean±SD	52.38±8.85	55.16±7.97	0.112
Range	35-73	40-75	
Sex			
Male	31 (62%)	25 (50%)	0.227
Female	19 (38%)	25 (50%)	
BMI, kg/m^2			
Mean±SD	28.32±3.08	27.33±4.86	0.225
Range	21.6-35.15	16.9-42.96	
WC, cm			
Mean±SD	90.02±13.24	91.56±13.92	0.571
Range	58.0-118.0	57.0-123.0	
Disease duration, yrs			
Mean±SD	8.64±3.15	19.92±4.72	<0.001
Range	2.0-16.0	2.0-26	

SD, standard deviation; VBMI, body mass index; WC, waist circumference, yrs, years.

Table 2. Clinical characteristics of diabetic patients with and without retinopathy.

Variables	Without retinopathy (n=50)	With retinopathy (n=50)	p
Past medical history			
Hypertension	12 (24%)	13 (26%)	0.817
Malignancy	4 (8%)	3 (6%)	0.695
FBS, mg/dL			
Mean±SD	177.24±40.04	199.64±57.04	0.025
Range	133-320	100-369	
HbA1c, %			
Mean±SD	8.48±1.3	9.65±2.36	0.003
Range	6.3-11.3	6.6-15.0	
Fasting insulin			
Mean±SD	14.35±4.7	19.35±4.7	0.005
Range	18.5-32.1	15.0-49.5	
HOMA-IR			
Mean±SD	6.29±2.61	9.22±5.59	0.001
Range	3.11-19.02	2.2-29.32	
CRP			
Mean±SD	2.19±1.36	4.75±3.4	<0.001
Range	0.85-7.1	1.03-14.6	

SD, standard deviation; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment-insulin resistance; CRP, C-reactive protein.

Diagnostic value of adiponectin

The ROC curve was used to explore the diagnostic value of APN in the context of the detection of DR. The area under the curve was 0.773, the 95% confidence interval was 0.679-0.867, and p<0.001. The sensitivity and specificity of the test at APN<3.0 ng/mL were 78% and 60%, respectively (Figure 2).

Correlation of adiponectin with other variables

Spearman's correlation test was used to examine the correlation of APN with other variables in patients with T2DM, whether having DR or not (Table 3). APN displayed a significant negative correlation with each of disease duration (r=-0.230, p=0.021), CRP (r=-0.251, p=0.044), fasting insulin (r=-0.221, p=0.027), and HOMA-IR (r=-0.223, p=0.019) as shown in Figures 3-6.

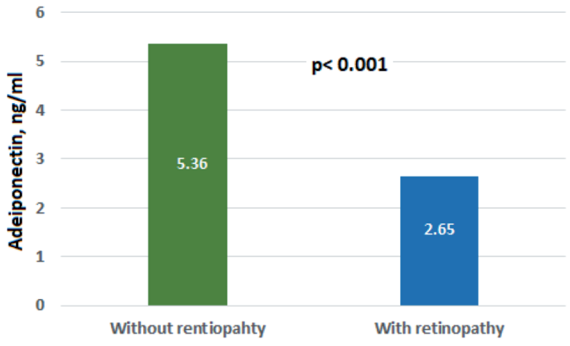

Figure 1. Median serum level of adiponectin in diabetic patients with and without retinopathy.

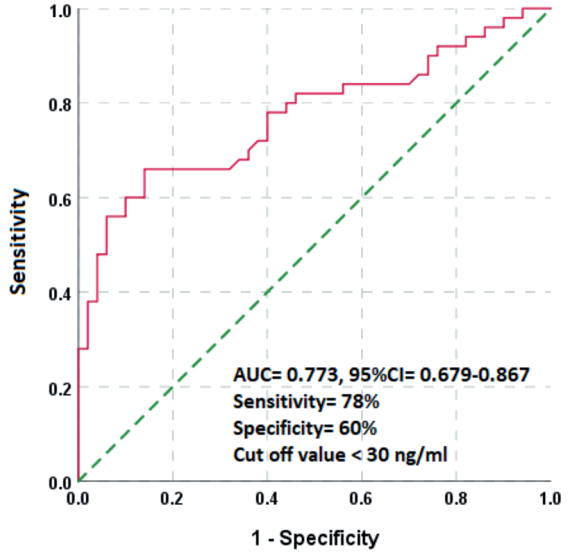

Figure 2. Receiver operating characteristic curve for adiponectin in the context of detecting diabetic retinopathy. AUC, area under the curve; CI, confidence interval.

Table 3. Spearman's correlation of adiponectin with other variables

Variables	Correlation coefficient	p
Age, years	0.001	0.996
Body mass index, kg/m^2	-0.084	0.408
Waist circumference, cm	-0.005	0.960
Disease duration, years	-0.230	0.021
Hemoglobin A1c, %	0.030	0.766
Fasting blood sugar, mg/dL	-0.193	0.055
C-reactive protein, mg/L	-0.251	0.044
Fasting insulin, µU/mL	-0.221	0.027
HOMA-IR	-0.223	0.019

HOMA-IR, Homeostatic Model Assessment-insulin resistance.

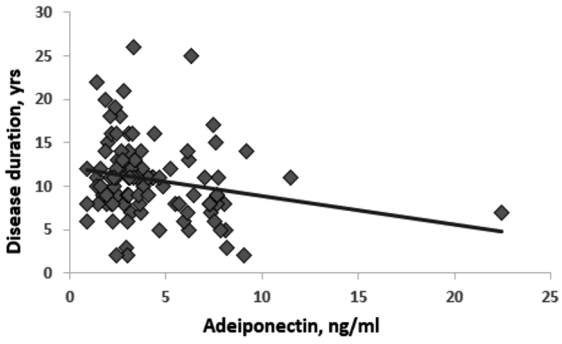

Figure 3. Scatter plot and regression line between adiponectin and type 2 diabetes mellitus duration.

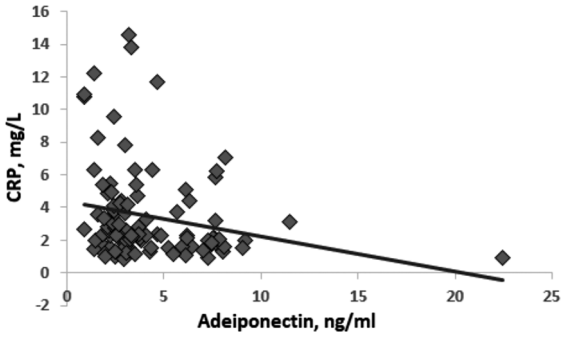

Figure 4. Scatter plot and regression line between adiponectin and C-reactive protein.

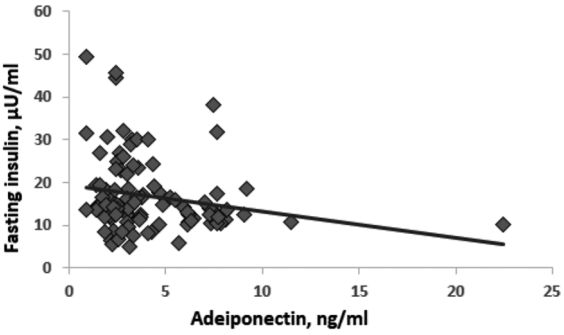

Figure 5. Scatter plot and regression line between adiponectin and fasting insulin.

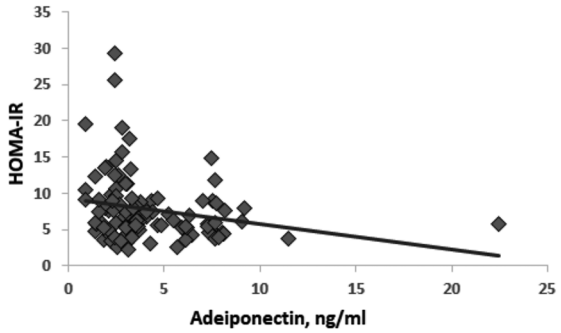

Figure 6. Scatter plot and regression line between adiponectin and Homeostatic Model Assessment-insulin resistance.

Discussion and Conclusions

In this study, patients with and without DR were closely matched in terms of baseline demographic characteristics such as age, sex, BMI, WC, and comorbid conditions, including hypertension and malignancy. The absence of significant differences in these variables indicates minimal selection bias and enhances the reliability of attributing observed clinical and biochemical variations to the presence or absence of DR.

A key finding was that patients with DR had a significantly longer duration of diabetes (19.92±4.72 years) compared to those without DR (8.64±3.15 years), with a highly significant p-value. This aligns with previous literature indicating that disease duration is a major risk factor for DR. Zhang *et al*. reported an 8% increase in DR risk with each additional year of diabetes.[14] A large observational study involving 4513 patients over 28 years showed a progressive increase in DR prevalence, from 6.6% among those with 0-5 years of diabetes to 63% among those with over 30 years of disease.[15] Likewise, another study revealed that the incidence of any type of DR markedly escalated with prolonged duration of DM.[16] This damage leads to heightened permeability, microvascular leakage, and the development of neovascularization and fibrosis in the retina. Ultimately, structural alterations may occur in retinal microvascular cells,[17] perhaps resulting in the total loss of capillaries. The concentration of vascular endothelial growth factor may correlate with the severity of DR.

Glycemic control also differed significantly between the groups. In the present study, patients with DR exhibited higher levels of FBS and HbA1c, both markers of poor glucose regulation. These findings corroborate extensive research demonstrating the link between hyperglycemia and DR progression. A study in the UK showed that lowering mean fasting blood glucose by 1.2 mmol/L through intensive therapy reduced DR progression.[18] A meta-analysis further revealed that intensive glycemic control decreased the need for retinal photocoagulation, reduced macular edema, and slowed DR progression.[19] Extensive clinical investigations demonstrated that sustained intensive glycemic control in both type 1 diabetes mellitus (T1DM) and T2DM substantially diminishes the risk of microvascular complications, such as DR.[20,21] Mechanistically, chronic hyperglycemia activates damaging cellular pathways such as the polyol pathway, leading to intracellular sorbitol accumulation, and enhances the formation of advanced glycation end-products. It also activates protein kinase C, increases oxidative stress, and upregulates inflammatory mediators, all contributing to endothelial dysfunction, increased vascular permeability, and blood-retinal barrier breakdown.[22] These processes collectively cause retinal ischemia, microaneurysm formation, and abnormal neovascularization.

IR, another hallmark of metabolic dysfunction in T2DM, was more pronounced in patients with DR, as indicated by higher fasting insulin and HOMA-IR values. Studies have shown that IR is not only a precursor to T2DM but also plays a direct role in vascular complications, including DR.[23,24] It is considered an independent predictor of DR, even after adjusting for glycemic control.[25] Recent advances in retinal imaging, such as optical coherence tomography angiography, have enabled the detection of early microvascular changes in patients with T2DM and IR, even before clinical signs of DR appear.[26] Moreover, IR has been associated with thinning of the retinal ganglion cell-inner plexiform layer, suggesting its role in retinal neurodegeneration.[27]

CRP, a systemic marker of inflammation, was significantly elevated in patients with DR in this study. Previous reports have shown elevated CRP levels in both T1DM and T2DM, and a strong association with the development of microvascular complications, including nephropathy, neuropathy, and retinopathy.[28] Higher CRP levels have been observed in patients with proliferative DR compared to those with non-proliferative forms.[29] Mechanistically, CRP contributes to retinal damage by increasing reactive oxygen species production and promoting pro-inflammatory cytokine expression *via* the CD32/NF-κB signaling pathway. This contributes to apoptosis of retinal cells and disruption of retinal function.[30] Several studies have reported higher APN levels in aqueous humor and serum in DR patients compared to controls.[31,32] A meta-analysis of 19 studies in Chinese populations found an inverse relationship between APN levels and DR severity,[33] while another analysis linked elevated APN to microvascular complications in T2DM.[34] However, contradictory findings also exist, indicating the need for further clarification of the role of APN in DR.[35,36]

In conclusion, this study reinforces the multifactorial pathogenesis of DR involving poor glycemic control, prolonged disease duration, IR, systemic inflammation, and reduced APN levels. Given the inverse correlation between APN and DR markers, APN may serve as a potential therapeutic target. Future research should explore interventions aimed at elevating APN levels, whether through pharmacologic agents, lifestyle changes, or biologics, and assess their impact on DR progression in high-risk populations.

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