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Evaluation of Fetuin-A level in diabetic retinopathy

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Abstract

Background: Diabetic retinopathy (DR) is a micro-vascular consequence of diabetes mellitus (DM) that manifests clinically as retinal ischemia, neovascularization, altered retinal permeability, and macular edema. In the adult population, DR is now considered a leading cause of blindness. Fetuin-A is a multifunctional glycoprotein that, because of its dual role in insulin resistance and angiogenesis, could be an early trigger of DR pathogenesis.

Objective: This study aimed to evaluate the level of Fetuin-A in diabetic patients with and without retinopathy and demonstrate if it could be used as an early indicator of DR.

Patients and methods: A case–control study enrolled 45 participants selected from Al-Zahraa University Hospital, between March 2021 and October 2021, they were divided into three groups: Group 1: healthy control group (n=15); Group 2: type 2 diabetic patients without DR (n=15); and Group 3: type 2 diabetic patients with DR (n=15). All groups were age- and sex-matched and were investigated by enzyme-linked immunosorbent assay (ELISA) to evaluate serum level of Fetuin-A.

Results: There was a highly significant difference of FBG, 2HPP, and HbA1c between the studied groups (p< 0.001), while there was no significant difference between the three studied groups regarding Fetuin-A. There were no significant correlation between Fetuin-A, glycemic parameters, and diabetic duration in Groups 2 and 3.

Conclusion: Fetuin-A has no significant role in the pathogenesis of diabetic retinopathy.

Keywords: DM, DR, T2DM, Fetuin-A

Introduction

Diabetic retinopathy (DR) is the most prevalent and serious ocular consequence of type 2 diabetes mellitus (T2DM), with symptoms evident in one third of T2DM patients at the time of diagnosis. After 20 years, more than 60% of patients with type 2 diabetes will acquire DR [1]. In individuals aged 20 to 74 years, the DR is one of the main causes of vision loss and preventable blindness worldwide, particularly in higher-income nations [2].

Fetuin-A is a multifunctional glycoprotein that is primarily released by hepatocytes in humans. Several potent angiogenic factors, including vascular endothelial growth factor (VEGF), which is involved in the pathophysiology of neo-vessels in DR can be stimulated by Fetuin-A. Fetuin-A is an endogenous inhibitor of insulin receptor tyrosine kinase that reduces insulin signaling and insulin resistance in the muscles and liver. Because of its dual role in insulin resistance, neovascularization, and angiogenesis, it could be an early indicator of DR pathogenesis [3].

Fetuin-A has been demonstrated to have pro-inflammatory effects in addition to promoting insulin resistance. Serum Fetuin-A levels were shown to be considerably greater in T2DM patients with vasculopathy than in those without vascular disease. Thus, Fetuin-A levels may be linked to vascularization as well as vessel shape and function [4]. We aimed to evaluate the level of

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Fetuin-A in diabetic patients with and without retinopathy and demonstrate if it could be used as an early indicator of DR.

Methodology

After approval of the ethical committee of the Faculty of Medicine for Girls, Al-Azhar University, and before enrollment in our study, all participants were informed in details about our study aim and signed consent. Adult patients of both sexes with T2DM were enrolled in this study.

Study design

This is a case-control study.

Study participants

This study was conducted on 45 participants aged from 25 to 60 years of both sexes. Patients were recruited from the Ophthalmology Department at Al-Zahraa University Hospital during the period between March 2021 and October 2021.

Inclusion criteria

Diabetic patients were diagnosed according to the criteria established by the American Diabetes Association (ADA) which are fasting blood glucose (FBG) $\geq$ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose (2-HPG) $\geq$ 200 mg/dL (11.1 mmol/L) or, random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) or, hemoglobin A1c (HbA1c) $\geq$ 6.5%.

Exclusion criteria

All patients known to have history of micro- and macro-vascular complications of DM other than DR. Also, patients suffer from any other ocular disease that may affect ocular circulation (e.g., glaucoma, age-related macular degeneration, and retinal vascular occlusion) or inherited macular disease. Patients with cardiovascular disease, stroke or transient ischemic attacks, liver disease, evidence of sepsis, and any autoimmune diseases as systemic lupus erythematosus were excluded.

The matching criteria

The controls were age- and sex-matched apparently healthy control.

All participants were subjected to the following:

- Clinical examination, complete medical, and ophthalmological history including the history of ocular disease, previous ocular trauma, or intraocular surgery.
- Best-corrected visual acuity (BCVA).
- Slit-lamp biomicroscopic examination.
- Fundus examination by slit-lamp biomicroscopy using + 90 D noncontact lens and indirect ophthalmoscopy. The presence or absence of DR was confirmed by fundus examination. All participants were subjected to following laboratory investigations.

Laboratory investigations included the following:

a. Complete blood count (CBC) was performed using fully automated hematology analyzer (Sysmex KX21N, Kobe, Japan).
b. Glycated hemoglobin (HbA1c), fasting blood sugar, and 2 h post-prandial (2HPP) were performed by fully automated chemistry analyzer Cobas c 311 (Germany).
c. Serum Fetuin-A level was performed by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions using Human Fetuin-A ELISA Kit (Cat. NO.E1386Hu), supplied by the Bioassay Technology Laboratory (China). This method used to quantify the level of human Fatuin-A with a detection range of 0.75–15 μmol/l.

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using the mean and standard deviation (SD) for normally distributed quantitative variables or median and interquartile range for non-normally distributed quantitative variables. Comparisons between groups were done using unpaired *t* test or analysis of variance (ANOVA) while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. Correlations between quantitative variables were done using Spearman correlation coefficient. *P* values $\leq$ 0.05 were considered as statistically significant, and $\leq$ 0.001 were considered highly significant.

Results

This study included 45 participants divided into three groups: Group 1: age- and sex-matched healthy subjects (n=15); Group 2: diabetic patients without retinopathy (n=15); and Group 3: diabetic patients with retinopathy (n=15). Demographic data of the three studied groups was illustrated in Table 1. Descriptive data of group 2 and group 3 was demonstrated in Table 2.

Comparison between the studied groups regarding the glycemic parameters and Fetuin-A was shown in Table 3. There was a highly significant difference of

Table 1 Demographic data of the studied groups

	Group 1 (healthy control) (*n*=15)		Group 2 (diabetic patients without retinopathy) (*n*=15)		Group 3 (diabetic patients with retinopathy) (*n*=15)	
Age: (year) *Mean ± SD*	54.33± 5.49		54.53 ± 5.97		55.33± 5.19	
	No	**%**	**No**	**%**	**No**	**%**
Sex						
Male	6	40.0%	7	46.7%	4	26.7%
Female	9	60.0%	8	53.3%	11	73.3%

SD Standard deviation

Table 2 Descriptive data of group 2 and group 3 regarding hypertension, diabetes treatment, and diabetic duration

		Group 2 (diabetic patients without retinopathy) (*n*=15)		Group 3 (diabetic patients with retinopathy) (*n*=15)	
		Count	**%**	**Count**	**%**
Hypertension	**Yes**	4	26.7%	6	40.0%
	No	11	73.3%	9	60.0%
Diabetic treatment	**Oral treatment**	12	80.0%	9	60.0%
	Insulin	2	13.3%	6	40.0%
	No treatment	1	6.7%	0	0.0%
Diabetic duration (years) Median (IQR)		4 (1–12)		15 (7–20)	

IQR Interquartile range

Table 3 Comparison between the studied groups regarding of glycemic parameters and Fetuin-A

	Group 1 Healthy control (*n*=15)	Group 2 Diabetic patients without retinopathy (*n*=15)	Group 3 Diabetic patients with retinopathy (*n*=15)	*P* value
FBG mg/dl Mean±SD	89.87±6.91	169±62.04	156.6±36.91	< 0.001
2HPP mg/dl Mean±SD	100.67±8.34	293.4±103.69	315.6±94.59	< 0.001
Glycated Hemoglobin A1c % Mean±SD	4.54±0.71	7.03±1.44	7.41±1.73	< 0.001
Fetuin-A mg/ml Median (IQR)	252.6 (157.7- 389)	308.2 (238.3- 389.8)	334.8 (274.2- 473)	0.098

FBG Fasting blood glucose, *2HPP* 2-h post prandial, *SD* Standard deviation, *IQR* Interquartile range

FBG, 2HPP, and HbA1c between the studied groups (p< 0.001). On the other hand, there was no significant difference between the three studied groups regarding Fetuin-A. A comparison between the studied groups was illustrated in Table 4.

Correlation between Fetuin-A and the studied parameters in diabetic patients without retinopathy (Group 2) and diabetic patients with retinopathy (Group 3) is summarized in Table 5. There were no significant correlations between Fetuin-A and studied parameters in both groups.

Discussion

Diabetic retinopathy is the most prevalent ocular complication of diabetes and one of the top causes of vision loss in adults globally. It is also one of the leading causes of preventable blindness. Early detection and treatment can prevent DR-related blindness [5].

Table 4 Comparison between the studied groups regarding the glycemic parameters and Fetuin-A

	P1 value	P2 value	P3 value
FBG mg/dl Mean±SD	< 0.001	< 0.001	1.0
2HPP mg/dl Mean±SD	< 0.001	< 0.001	1.0
Glycated Hemoglobin A1c % Mean±SD	< 0.001	< 0.001	1.0
Fetuin-A mg/ml Median (IQR)	NS	NS	NS

Abbreviations: *P1*, *P* value between group 1 and group 2; *P2 P*, value between group 1 and group 3; *P3 P*, value between group 2 and group 3; *FBG*, fasting blood glucose; *2HPP*, 2-h post-prandial; *SD* Standard deviation, *IQR* Interquartile range, *NS* Non-significant, *SD* Standard deviation, *IQR* Interquartile range

However, retinal examinations are frequently postponed or overlooked until severe damage or even vision impairment has occurred. As a result, early detection of microvascular problems may allow for early detection of pathogenic alterations, stopping, following up, or even delaying the start of T2DM and improving T2DM prognosis [6]. The goal of this study was to determine the Fetuin-A level as a marker that may help in the early diagnosis of DR.

We observed a highly significant difference in FBG, 2HPP, and HbA1c between the studied groups ($p<$ 0.001). This was in agreement with Al-Said et al. [7], who found a significant difference in the mean levels of FBG in the diabetic without complications group versus the DR group. But in contrast to our study, Al-Said et al. [7] concluded that there were no significant differences were detected in the mean levels of 2HPP between the diabetic without complications group and the DR group. This may be attributed to the poor glycemic control and lifestyle changes of the studied patients.

On the other hand, our study observed that there were no significant differences between the three studied groups regarding Fetuin-A. Our results coincided with Al-Said et al. [7], who showed that there was a non-significant increase in the mean levels of Fetuin-A in patients with DR compared with diabetic patients without micro-vascular complications. On the other hand, serum Fetuin-A levels showed no significant difference between patients with T2DM and controls [5]. Also, Jung et al. [8] reported that mean serum Fetuin-A levels were not significantly different in T2DM patients with and without DR. Mori et al. [9] found no significant difference in serum Fetuin-A levels between type 2 diabetic and non-diabetic groups.

In contrast to our study, El-Deeb et al. [10] reported that T2DM patients had a significantly higher level of Fetuin-A in comparison with non-diabetic control. Also, Song et al. [11] reported that higher Fetuin-A concentrations were associated with type 2 diabetes and insulin resistance. Also, Keskin et al. [12] reported a significant increase in Fetuin-A levels in type 2 diabetes patients when compared to non-diabetics.

Conclusion

Fetuin-A has no significant role in the pathogenesis of DR. But it may play a role in progression of the disease. Further studies correlating Fetuin-A with DR stage are recommended. The glycemic markers (FBG, 2HPP, and HbA1c) and diabetic duration may have important role in the pathogenesis of DR. Further studies with a larger sample size can help to verify our results.

Table 5 Correlation between Fetuin-A and the studied parameters in group 2 and group 3

		Group 2 Diabetic patients without retinopathy (*n*=15)	Group 3 Diabetic patients with retinopathy (*n*=15)
		Fetuin-A mg/ml	Fetuin-A mg/ml
Diabetic duration (years)	**Correlation coefficient**	0.316	−0.145
	***P* value**	0.251	0.607
FBG mg/dl	**Correlation coefficient**	−0.034	0.132
	***P* value**	0.904	0.638
2HPP mg/dl	**Correlation coefficient**	−0.218	0.321
	***P* value**	0.435	0.243
Glycated hemoglobin A1c %	**Correlation coefficient**	−0.252	0.366
	***P* value**	0.364	0.179

FBG Fasting blood glucose, *2HPP* 2-h post-prandial

Abbreviations
DR: Diabetic retinopathy; T2DM: Type 2 diabetes mellitus; VEGF: Vascular endothelial growth factor; ADA: American Diabetes Association; FBG: Fasting blood glucose; 2-HPG: Two-hour plasma; HbA1c: Hemoglobin A1c; BCVA: Best-corrected visual acuity; CBC: Complete blood count; 2HPP: 2 hours postprandial; SD: Standard deviation; IQR: Interquartile range.

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Authors' contributions
EA has a major role in collecting the data and laboratory investigations of the patients in the study, BA made substantial contributions to the design of the work, the analysis, interpretation of data, and a major contributor in revising the manuscript. SM is the corresponding author and made substantial contributions to the analysis, interpretation of the laboratory data, and a major role in writing the manuscript. AM has a major role in doing the ophthalmologic examination and fundus photography of the patients in the study. The authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study's protocol was approved by the Research Ethics Committee of the Faculty of Medicine for Girls Al-Azhar University. Informed written consent was obtained from all participants.

Consent for publication
Applicable
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Competing interests
The authors declare that they have no competing interests.

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