Ischemia-modified albumin relation to glycemic state, neuropathy, and retinopathy in patients with type2 Diabetes mellitus

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Abstract

Background: The incidence of microvascular complications is rising although there is improvement in glycemic control, dyslipidemia, and hypertension treatment. Early identification of patients with a high risk of developing vascular complications helps in their prevention. There is a strong need for biomarkers for use in the early detection of microvascular complications. Ischemia-modified albumin (IMA) is formed when ischemia of the hypoxic tissue induces modification of circulating albumin. IMA is a sensitive marker of tissue hypoxia and oxidative stress.

Objectives: to evaluate the relationship of IMA to glycemic state and its ability to predict microvascular complications of diabetic neuropathy (DN) and diabetic retinopathy (DR) in type 2 DM patients.

Patients and methods: 100 Participants were divided into three groups:
Group A: (n=35) complicated type 2 diabetic patients (with neuropathy, retinopathy, or both). GroupB: (n=35) non-complicated type 2 diabetic patients, GroupC: (n=30) control group (healthy individuals).

Results: Using the ROC curve of IMA in predicting diabetic neuropathy and retinopathy, showed high sensitivity, the area under the curve (AUC) is 0.948 (95% CI 0.885:0.983), p <0.0001, cutoff point>95.7 U/ml (sensitivity =100%, specificity =95.7%, PPV =74.3%, and NPP =100%), ROC curve of IMA in predicting diabetic retinopathy the AUC is 0.960 (95% CI 0.900:0.989), p <0.0001, cutoff point>110.5 U/ml (sensitivity =100%, specificity =94.4%, PPV =87.9%, and NPP=100%).

Conclusion: Ischemia-modified albumin levels were significantly higher in patients with DN and DR.

Keywords: Diabetic retinopathy; Diabetic neuropathy; Ischemia-modified albumin.
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Introduction

There is a going risk of diabetic microvascular complications including DR and DN is the main cause of diabetic foot disease and amputations. The prevalence of peripheral neuropathy is estimated between 6% and 51% among adults with diabetes according to glucose control, diabetes mellitus duration, and age of the patients, The clinical manifestations range from asymptomatic to painful neuropathic symptoms. The incidence of microvascular complications is rising although there is improvement in glycemic control, dyslipidemia, and hypertension treatment**(McKay et al., 2016).** Early identification of patients with a high risk of developing vascular complications helps in their prevention, at the early stages of complications the tissues can respond better to treatment. There is a strong need for biomarkers for use in the early detection of microvascular complications **(Forbes and Fotheringham, 2017).** First identified in the early 1990s, IMA is produced when ischemia stresses released from hypoxic heart tissue induce modification of circulating albumin. IMA is a sensitive marker of tissue hypoxia and oxidative stress. The (N-terminal) of the albumin molecule is a binding site for transitional metals such as cobalt. During ischemia, the N-terminus of albumin is altered, possibly as the result of hypoxia and acidosis decreasing its binding capacity for metals **(Shevtsova et al., 2021**). We aimed to evaluate the relationship between ischemia-modified albumin and the glycemic state and its ability to predict microvascular complications (DN, DR) in type 2diabetic patients.

Patients and methods

This cross-sectional study was conducted in Sohag University Hospital, Internal Medicine Department, Sohag Faculty of Medicine. In the period between January 2019 and December 2021. The study was approved by the ethics committee and informed written consent was taken from all participants. 100 Participant were divided into three groups. The sample size of 30 patients in each group was a convenience sample based on the mean of ischemia-modified albumin from a previous study done by (**Saleh et al., 2019**) with a type I error of 0.05 and a power of 80%. The number of participants was increased to 35 patients in the non-complicated diabetic group and complicated diabetic group to compensate for expected dropouts.

Group A: (n=35) complicated type 2 diabetic patients (either diabetic neuropathy (DN) diabetic and/or retinopathy (DR); **Group B:** (n=35) non-complicated type 2 diabetic patients; **Group C:** (n=30) control group (healthy individuals).

The participants were of both gender and aged 40 to 75 years. The study participants were evaluated regarding microvascular complications mainly (DN and DR). The diagnosis was confirmed by history and neurological examination and classified using the following classification: 1) Generalized symmetric polyneuropathies: Chronic sensorimotor (typical diabetic peripheral neuropathy (DPN), acute sensory, and autonomic. 2) Focal and multifocal neuropathies: cranial, truncal, focal limb, proximal motor (amyotrophy), and co-existing chronic inflammatory demyelinating

polyneuropathy (CIDP) **(Boulton et al., 2005)**.

All the studied individuals were subjected to the followings; Full History taking, medication history of anti-diabetics, peripheral neuropathy, and other illness if present, Full clinical examination including fundus examination and neurological examination including:

Mental state, cranial nerves,sensory-negative or positive, diffuse or focal; usually insidious in onset and showing a stocking-and-glove distribution in the distal extremities motor-distal, proximal, or more focal weakness, sometimes occurring along with sensory neuropathy (sensorimotor neuropathy). Autonomic neuropathy testing: assess supine and upright blood pressure and heart rate.

A venous blood sample of 2cm after fasting 12 hours for a lipid profile test and another 2cm of venous blood was taken on an EDTA tube for HbA1c.

Exclusion criteria: diabetic nephropathy was excluded by urinary microalbuminuria test, Patients with liver dysfunction, patients with ischemic events like acute myocardial infarction or stroke within the last three months, a patient who has any infection in the last 6 weeks, patients with malignancy, patients receiving corticosteroid therapy, patients with type1 DM, and patients with renal failure.

Specimen requirements: The levels of serum IMA were measured using a South Korean commercial kit Sino Gene Clon Biotech Co., Ltd cat no: SG10656. The blood was left to clot at room temperature for 10-20 min, then centrifuged at the speed of 2000-3000 rpm for 20-min. The serum was separated and stored at -20°C or -80°Cuntil the time of assay.

Statistical analysis

Data were analyzed using STATA version 14.2. Quantitative data were represented as mean and standard deviation. Data normality was tested by the Kolmogorov–Smirnov test and was analyzed using student t-test to compare the means of two groups and ANOVA for comparison of the means of three groups. Pearson correlation analysis was done to test the linear relationship between variables. The utility of IMA to assess the presence of either diabetic neuropathy and/or retinopathy was performed by receiver operating curve (ROC) curve to measure the area under the curve (AUC) to detect the best cutoff value of IMA, sensitivity, specificity, positive predicted value (PPV) and negative predictive value (NPV). The P-value is considered significant, if < 0.05.

Results

Group A: (n=35) (19 females and 16 males), complicated type 2 diabetic patients (with one or more microvascular complications), with a mean age of 53.6±6.98 years; Group B: (n=35)(15 females and 20 males),non-complicated type 2 diabetic patients with the mean age 52.6±6.39 years; Group C: (n=30) (16 females and 14 males), control group (age and sex-matched healthy individuals)with the mean age: 52.97±7.24 years.

The lipids (cholesterol, triglycerides, LDL) levels were significantly higher in group A (DN & DR) than group B (without microvascular complications) with P<0.0001, also significantly higher in group B (without microvascular complications)

versus control group with p < 0.0001 HDL levels were significantly higher in the control group than group A (with microvascular complications) with p<0.0001 (**Table .1**).

Table 1. Demographic data of the studied groups

Variable	**Complicated DM N=35**	**Non-complicated DM N=35**	**Controls N=30**	**P-value**
Age/years Mean ± SD	53.6±6.98	52.6±6.39	52.97±7.24	0.83
Gender Female Male	19 (54.29%) 16 (45.71%)	15 (42.86%) 20 (57.14%)	16 (53.33%) 14 (46.67%)	0.58
Diabetic treatment				
Combined oral hypoglycemic (metformin and sulfonylureas)	14 (40%)	24 (68.5%)		0.001
Insulin	21 (60%)	11 (31.4%)		0.001
Compliance to antidiabetics	8(23%)	16 (44%)		0.01
Neuropathic pain treatment				
Gabapentin	27(78%)			0.001
Duloxetine	7 (20%)			0.01
Glycemic control				
Poor glycemic control (>7%)	100%	33(94.28%)		0.01
Good glycemic control (<7%)	(0)0%	2 (5.71 %)		0.01

ANOVA test: P value compared the three groups, student t test*for comparing two groups

IMA levels were significantly higher in all diabetic patients than in the control group with p <0.0001. Levels of IMA are significantly higher in group A (122.47±7.23) than in group B (79.60±7.76) which is also higher than group C (41.79±1.54) with P <0.0001(**Table.2**). The distribution of microvascular complications (DN, DR) is recorded in (**Table.3**).

Table 2. Neurological and fundus examination findings

Neurological evaluation findings	No (%)
Generalized symmetric polyneuropathies: • Numbness, tingling • Chronic symmetrical sensorimotor neuropathy with glove and stock pattern • Muscle weakness	 35(100%) 35(100%) 11 (31.42%)

Fundus examination	No (%)
Diabetic proliferative retinopathy	12 (34.28%)
Advanced eye disease (retinal detachment)	3 (8.7%)
Pre proliferative retinopathy (areas of ischemia).	4 (11.42%)

Table 3. Laboratory data of the studied groups

Variable (Mean ± SD)	Complicated DM N=35	Non-complicated DM N=35	Controls N=30	P-value
HbA1c %	10.07±1.57	8.00±1.07	5.39±0.31	<0.0001
Cholesterol (mg/dl)	283.6±42.52	208±28.92	184.87±16.23	<0.0001
Triglyceride (mg/dl)	199.8±17.05	169.74±11.75	145.13±20.38	<0.0001
LDL (mg/dl)	158.23±22.47	130.97±19.47	107.33±17.22	<0.0001
HDL (mg/dl)	28.31±7.52	35.2±7.64	41±8.5	<0.0001
IMA (U/ml)	122.47±7.23	79.60±7.76	41.79±1.54	<0.0001

ANOVA test: P value compared the three groups,

There were significantly higher mean values of HbA1c, cholesterol, triglycerides, LDL, IMA among complicated DM than both non-complicated DM and the control groups, $p<0.05$ for all **(Table.4)**, although the mean level of IMA wasn't differ in term of the type of diabetic complication **(Table.5).**

Table 4.Laboratory data of the studied population

Variable (Mean ± SD)	**Complicated DM, N=35**	**Non-complicated DM, N=35**	**Controls N=30**	**P1**	**P2**	**P3**
HbA1c %	10.07±1.57	8.00±1.07	5.39±0.31	<0.0001	<0.0001	<0.0001
Cholesterol (mg/dl)	283.6±42.52	208±28.92	184.87±16.23	<0.0001	<0.0001	0.01
Triglycerides (mg/dl)	199.8±17.05	169.74±11.75	145.13±20.38	<0.0001	<0.0001	<0.0001
LDL (mg/dl)	158.23±22.47	130.97±19.47	107.33±17.22	<0.0001	<0.0001	<0.0001
HDL (mg/dl)	28.31 ±7.52	35.2±7.64	41 ±8.5	<0.0001	<0.0001	0.27
IMA (U/ml)	122.47±7.23	79.60 ±7.76	41.79±1.54	<0.0001	<0.0001	<0.0001
Duration	12.8±5.76	6.85±2.08	-	<0.0001	-	-

Student t-testP1 compared complicated DM with uncomplicated DM, P2 compared complicated DM with controls, and P3 compared non-complicated DM with controls.

Table 5.Distribution of IMA by different diabetic complications

Complications	**No (%)**	**IMA level**
Diabetic neuropathy	26(74.28%)	120.67±6.55
Diabetic retinopathy	19(54.28%)	121.74±5.52
Diabetic neuropathy + Diabetic retinopathy	5(14.28%)	121.74±5.52

IMA was positively significantly correlated to lipid profile in diabetic patients, while in the control group there was an insignificant positive correlation (**Table.6).** The ROC curve demonstrated that the IMA cutoff value and the AUC had a good predictive value for the prediction of microvascular complication (DN and DR) (**Fig.1, 2**).

Table 6. Correlation of IMA and enlisted variable

Variable	Complicated DM		Non-complicated DM		Controls		All diabetic patients	
	r	P	r	P	r	P	R	P
HbA1c	0.71	0.001	0.70	0.001	0.36	0.051	0.66	<0.0001
Cholesterol	0.67	<0.0001	0.55	0.001	0.26	0.001	0.76	<0.0001
Triglyceride	0.42	0.01	0.38	0.001	0.29	0.02	0.73	<0.0001
LDL	0.63	0.0001	0.41	0.02	0.24	0.64	0.66	<0.0001
HDL	-0.05	0.80	-0.08	0.54	-0.09	0.15	-0.42	0.0002

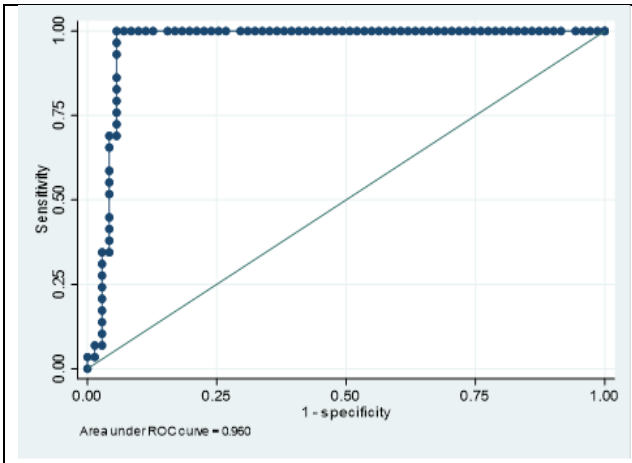

Fig. 1. ROC curve of IMA in predicting diabetic neuropathy. The AUC is 0.948, (95% CI 0.885:0.983), p<0.0001, cutoff point > 95.7 U/ml, sensitivity = 100%, specificity = 95.7%, PPV =74.3%, and NPP =100%.

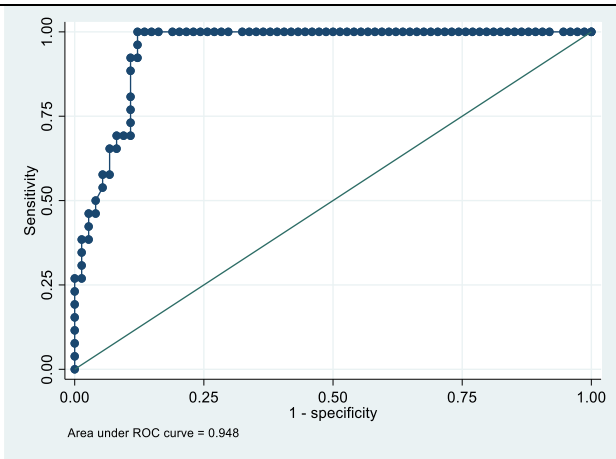

Fig. 2. ROC curve of IMA in predicting diabetic retinopathy. The AUC is 0.960, (95% CI 0.900:0.989), p<0.0001, cutoff point >110.5 u/ml, sensitivity =100%, specificity =94.4%, PPV=87.9%, and NPP=100%.

Discussion

In our study, the IMA In the present study there was a positive correlation between IMA and DN this was in agreement with **(Ozkan et al., 2021)** who studied DN and related foot ulcers, measured the serum IMA levels in the diabetic foot ulcer patients and compared to diabetic patients without diabetic foot and control group, the levels of IMA were significantly higher in diabetic foot ulcer than in the diabetic patients without foot ulcer and control groups. Our study showed that IMA could help in detecting DN with sensitivity =100%, specificity =95.7%, by using the ROC curve, AUC is 0.948 (95% CI 0.885:0.983), p

<0.0001, cutoff point>95.7 U/ml, PPV=74.3%, and NPP=100%). The present study showed that IMA had a significant positive correlation with diabetic retinopathy p=001, this was in agreement with (**Turk et al., 2011; Kirboga et al., 2014; and Kumar et al., 2022**)concluded that IMA may be used as an effective and novel screening biomarker for assessing oxidative stress associated with DR, this agreed with a meta-analysis investigated the relationship between the IMA and DR in control and diabetes mellitus patients **(Reddy et al., 2016).**

Our study showed that IMA could help in detecting DR with sensitivity =100%, specificity =94.4%, by using the ROC curve, AUC is 0.960 (95% CI 0.900:0.989), p<0.0001, cutoff point >110.5 U/mlPPV=87.9%, and NPP=100%. These results showed that the serum IMA could detect DR in diabetic patients.

IMA levels were higher in patients with poor glycemic control (HbA1c ≥ 7) than in those with HbA1c<7%. IMA had a good correlation with HbA1c levels, these results agreed with **(Refaat et al., 2014)**who found a significant positive correlation of serum IMA to HbA1C in patients with type 2 DM. Similar finding by**(Piwowar et al., 2008).** our study showed a significant positive correlation between serum LDL, cholesterol and triglycerides, and serum IMA. similar results were reported by (**Saleh, et al2019).** The present study found that there was a negative correlation between IMA and HDL, which agreed with **(Said et al., 2018)**, these results agreed with **(Refaat et al., 2014)** who found a positive correlation between IMA levels and total cholesterol, LDL-cholesterol as well as HDL-cholesterol in dyslipidemia and non-dyslipidemia diabetic patients. In contrast to our study (**Piwowar et al., 2008**) study had shown a weak correlation between LDL-cholesterol and IMA, similarly **(Chawla et al., 2016)** concluded that the high LDL showed lower IMA levels.

Conclusion

Ischemia-modified albumin levels were significantly higher in type 2 diabetic patients with microvascular complications (DN, DR). IMA could be used as a risk marker for detecting diabetic neuropathy and diabetic retinopathy.

Study limitations : There are two major limitations in this study, that could be addressed the first, the limited number of hospital-based cases, the second, the cross-sectional design. A further longitudinal study with a larger number of cases was needed.

Declarations: Ethical approval: approval of the study proposal was obtained from the Institutional Review Board of the Faculty of Medicine, Sohag University, Egypt.

Approval and consent to participate: written informed consent was taken from all participants.

Consent for publication: The final draft of the manuscript was read and approved by all authors before submission.

Competing interests: No conflict of interest as declared by the authors.

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Authors' contributions: Ahmed AA, is the principal investigator, prepared the idea of

the work and reviewed the statistics, formulated the results, wrote the discussion, and did the final edits, responsible for writing the discussion and statistics, Noreldin AK, is responsible for data acquisition and review search, revised the statistics and data collection. The final manuscript was revised and accepted by all authors.

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