The role of ischemia modified albumin in detecting diabetic nephropathy

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Abstract

Background: Ischemia-modified albumin (IMA) is considered a marker of oxidative stress and ischemia.

Objectives: In this study, we aimed at establishing an association between IMA and diabetic nephropathy (DN) in type2 Diabetes mellitus (T2DM) patients.

Patients and methods: One hundred individual participated in the study.70 T2DM patients, 35 in group A had DN, 35 in group B without DN and 30 healthy individuals, group C as a control group. We used urinary microalbuminuria test and urinary albumin creatinine ratio for assessment of diabetic nephropathy.

Results: plasma levels of IMA were higher in T2DM with DN ((122.47±7.23) u/ml than in T2DM without DN(79.60±7.76) u/mlwho were higher than the control group (41.79±1.54)u/ml, p <0.0001.there was positive correlation between IMA and RBG(r=0.72), p=0.001), HBA1c(r=0.71, p=0.001),urinary microalbuminuria(r =0.61,p =0.001),urinary albumin/creatinine ratio(r =0.68, p =0.01) and creatinine(r =0.5,p =0.01) in group A T2DM with DN.ROC curve had high sensitivity and specificity for detecting diabetic nephropathy, the area under curve (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% NPP=100%).

Conclusion: The ischemia modified albumin levels were significantly higher and positively associated with the duration of diabetes, RBS and HbA1c levels in T2DM patients with nephropathy. IMA could be used as a risk marker for Type 2 diabetic nephropathy.

Keywords: Ischemia modified albumin; Diabetes Mellitus; Random blood glucose; Diabetic nephropathy**.**

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Introduction

Diabetes mellitus (DM) is one of the commonest endocrine disorders manifested by chronic hyperglycemia, which causes many microvascular complications including diabetic nephropathy **(ADA, 2011).** DN is characterized by decrease in both the albumin excreted in urine and the glomerular filtration rate (GFR) **(Andy et al., 2014)**.High blood pressure, insulin resistance and vascular inflammation are risk factors that cause endothelial damage and dysfunction leading to atherosclerosis (**Mogensen. et al 1994).**

Many markers such as hyper-homocysteine, microalbuminuria and high sensitive C-reactive protein (hs-CRP) lead to the endothelial dysfunction, their intensity is a powerful predictive factor of macrovascular disease.**(Perticone. al 2001)**.

Type 2 diabetic patients may suffer from renal failure as a consequence of DN which is considered as serious microvascular complications of DM. IMA considered a marker of damage to the endothelial cells, is formed when ischemia of the human tissues due to hypoxia and oxidative stress causes modification in the N-terminal amino acids of the serum albumin. **(Dekker, et al 2010).**

Patients and methods

This cross sectional study conducted in Sohag University Hospital, Internal Medicine Department, after approval of the Institutional Review Board (IRB) and informed written consents from all participants. In the period between January 2019 and December 2021.The participants were of both gender and aged 40 to 75 years. We excluded from the study patients with liver dysfunction, patients who suffered from ischemic events, in the last three months, like acute myocardial infarction or cerebrovascular stroke, patient who has any infection in last 6week, patients with malignancy and patients on steroid medications.

Participants were divided into three groups Group A : (n=35) T2DM with DN . Group B: (n=35) T2DM without DN and Group C: (n=30) control group (healthy individuals). The study participants were evaluated regarding microvascular complications mainly (nephropathy). After taking history from all participants, they were clinically examined with measurement of blood pressure (B.P) and body mass index (BMI).

Blood samples (5cm venous blood) and fresh urine samples collected first thing in the morning . Ischemia modified albumin (IMA). HBA1c, random blood glucose, serum creatinine, urinary Micro albumin and urinary albumin/creatinine ratio were estimated. The levels of serum IMA were measured using a South Korean commercial kit Sino Gene Clon Biotech Co.,Ltd cat no :SG10656. The Serum is left for 10 to 20 minutes to coagulate at room temperature, after centrifugation of the sample for 20 minutes at a speed of 2000-3000 rpm, the supernatant was removed then centrifugation was repeated in case of precipitation, then samples were stored at - 20°C or -80°C.

Statistical analysis

STATA version 14.2 was used to analyze the data.Chi square test was used to compare qualitative data which were presented as numbers and percentage. Pearson correlation

for correlating IMA with different variables was done. ANOVA was used to compare the means of three groups (**Tables 1,3,4**). When the data was not normally distributed Kruskal Wallis test was used for comparison of three groups and Mann-Whitney test to compare two groups for microalbuminuria, UAC ratio, and creatinine test and for duration of diabetes (**Tables1,2,4**). Roc curve analysis was used to detect best cutoff. Sensitivity, specificity, positive predicted value (PPV) and negative predictive value(NPV) were also calculated. When p-value 0.05 or less was considered significant. Excel program where used to produce graphs.

Results

Regarding to the clinical data of the studied groups, Group A (DM with nephropathy) had significant longer duration of diabetes p=0.001 had longer duration of diabetes, most of them more than ten years duration with significant p= 0.001,while group B (without nephropathy)had shorter duration, most of them range from 5 to 10 years duration with significant p = 0.001.The BMI was elevated in both group A and group B of the patients with BMI higher in group A (with nephropathy) than control group with significant p=0.001, group B (without nephropathy) higher than control group with significant p= 0.02**.**The demographic and clinical data recorded (**Table 1**).

Table 1: Demographic and clinical data of the studied groups

Variables	Type2 DM With DN N=35	Type 2 DM Without DN N=35	Controls N=30	P value	P1	P2	P3
Age/years Mean ± SD	53.6±6.98	52.6±6.39	52.97±7.24	0.83	1.00	1.00	1.00
Gender Female Male	19 (54.29%) 16 (45.71%)	15 (42.86%) 20 (57.14%)	16 (53.33%) 14 (46.67%)	0.58	0.34	0.94	0.40
Duration of DM Mean ± SD	12.8±5.76	6.85±2.08		0.001	0.001	0.001	
BMI Mean ± SD	28.25±3.38	27.25±2.58	25.41±1.78	0.0002	0.38	0.001	0.02
HTN No Yes	13 (37.14%) 22 (54.29%)	16 (45.71%) 19 (42.86%)		0.001	0.01	0.001	
Systolic bl. pressure Mean ± SD	137.57±13.63	136.46±12.14	126.6±9.93	0.0007	1.00	0.001	0.004

Diastolic bl. pressure Mean ± SD	**81±6.95**	**80.36±6.80**	**78.17±6.23**	**0.17**	**1.00**	**0.28**	**0.33**

ANOVA test :P value compared the three group,(P1 with and without nephropathy), P2 (compared nephropathy with controls), P3(without nephropathy and control)

The laboratory data of the studied groups were recorded in **(Table 2**).

Table2 : Laboratory Data of the studied population

Variables	Type DM With DN N=35	Type 2 DM Without DN N=35	Controls N=30	P value	P1	P2	P3
Random bl. sugar (mg/dl) Mean ± SD	**270.86± 44.15**	**215.34± 24.85**	**102.17± 11.17**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
HbA1c% Mean ± SD	**10.07± 1.57**	**8.00± 1.07**	**5.39± 0.31**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
MA (mg/dl) Mean ± SD	**177.03± 96.90**	**63.09± 17.13**	**9.63± 3.07**	**0.0001**	**0.0001**	**0.0001**	**0.0001**
UAC ratio Mean ± SD	**1.28± 0.33**	**0.61± 0.31**	**0.06± 0.02**	**0.0001**	**0.0001**	**0.0001**	**0.0001**
Creatinine (mg/dl) Mean ± SD	**1.17± 0.36**	**0.81± 0.20**	**0.72± 0.18**	**0.0001**	**0.0001**	**0.0001**	**0.11**
IMA (U/ml) Mean ± SD	**122.47±7.23**	**79.60 ±7.76**	**41.79 ±1.54**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

.Kruskal Wallis test was used for comparison of three groups and Mann-Whitneyto compare two groups for microalbuminuria(MA), UAC ratio, and creatinine tests.

The glycemic state of the Diabetic patients (group A,B) were recorded in (**Table 3**).

Table3: Glycemic state of the Diabetic patients.

Glycemic state	Good glycemic state (HbA1C) (<7%)	Poor glycemic state (HbA1C) (>7%)
Group A (with nephropathy)	**0 patients**	**35 patients (100%)**
Group B (without nephropathy)	**2 patients (5 .7%)**	**33 patients (94.3%)**

The levels of IMA are higher in group A (122.47±7.23) than group B (79.60±7.76) which is also higher than group C (41.79±1.54) with P values <0.0001 which is statistically significant **(Fig. 1).**

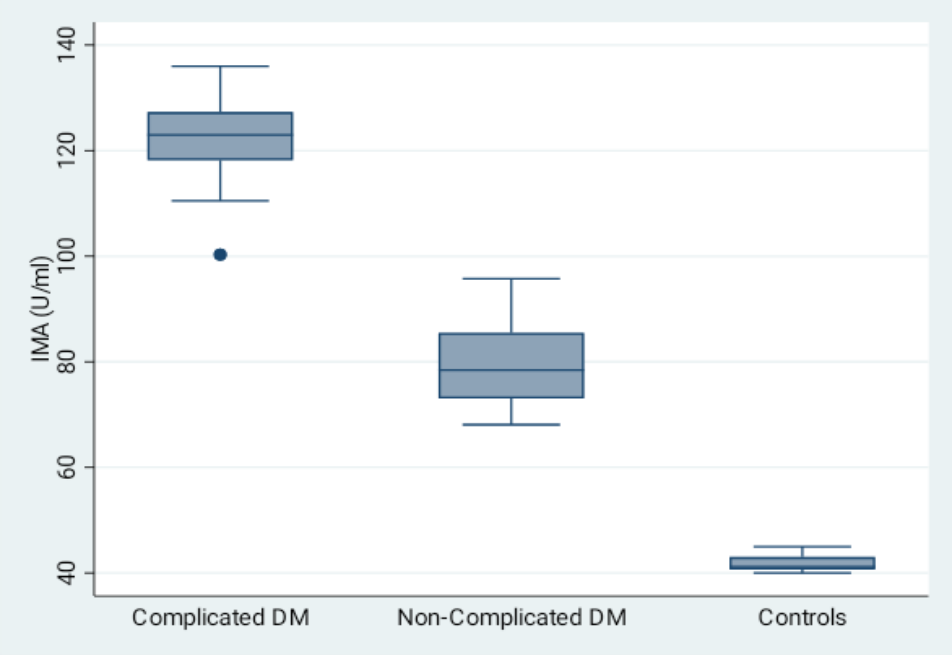

Figure 1:Ischemia modified albumin in different groups

This study results showed insignificant negative correlation between IMA and the age of all the study participants. Positive correlation between IMA and duration of diabetes was shown in both groups (A, B) of diabetic patients, with moderate correlation (0.55) with group A (with nephropathy) and weak correlation (0.35) with group B (without nephropathy) with significant p value <0. 0001 (**Table 4)**.The IMA had a insignificant positive correlation with BMI in both T2DM groups while in the control group with increased BMI there was positively correlation with IMA with a p = 0.0002 .There was a positive correlation between IMA and hypertension in both group A (T2DM with DN) and group B (T2DM without DN) patients P = 0.001.

Correlating IMA with RBS and with HBA1C showed positive strong correlation in group A (with nephropathy) and in group B (without nephropathy) with p value <0.0001, while control group showed positive weak correlation **(Table. 4).**Regarding renal function there was a positive moderate correlation between IMA and microalbuminuria, urinary A/C ratio and creatinine in both group A, B with significant p value <0.01, while control group had weak correlation with non-significant p value (**Table.4)**.

Table4 : Correlation of ischemia modified albumin and enlisted variable

Variables	With DN		Without DN		Controls		Diabetic patients	
	R	P	R	P	R	P	R	P
Age	-0.13	0.43	-0.09	0.61	-0.34	0.07	0.03	0.78
Duration of DM	0.55	0.05	0.34	0.046			0.59	<0.0001
BMI	0.14	0.43	0.005	0.98	0.62	0.0002	0.18	0.14
HTN	0.75	0.001	0.73	0.001				
RBS	0.72	0.001	0.71	0.001	0.14	0.46	0.67	<0.0001
HbA1c	0.71	0.001	0.70	0.001	0.36	0.051	0.66	<0.0001
MA	0.61	0.001	0.42	0.001	0.32	0.08	0.62	<0.0001
UAC ratio	0.68	0.01	0.35	0.04	0.37	0.67	0.75	<0.0001
Creatinine	0.5	0.01	0.44	0.01	0.22	0.23	0.48	<0.0001

Using the receiver operating characteristic curve (ROC curve)with a cut off value and area under the curve, IMA has a good predictive value for the prediction of microvascular complication (nephropathy) with high sensitivity and specificity as shown in (**Fig.2**).

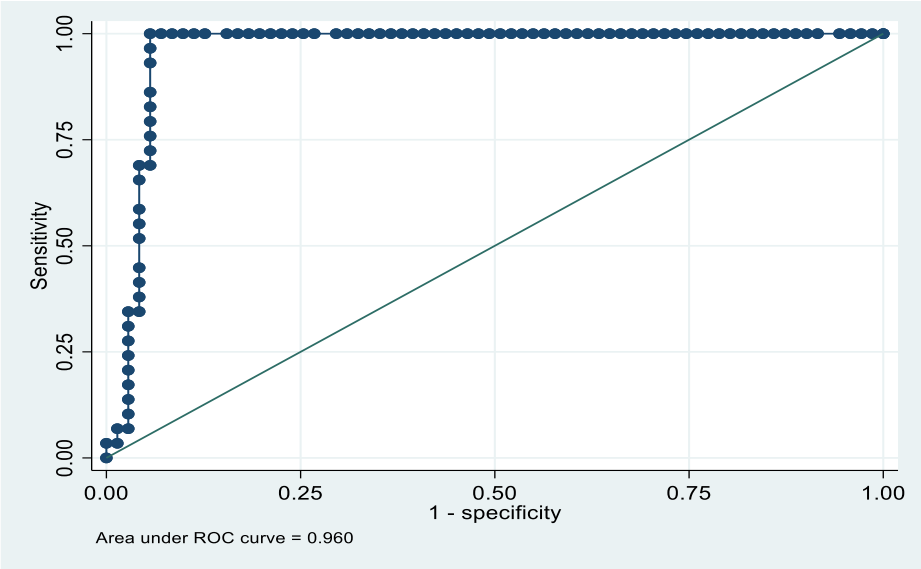

Figure 2.ROC curve of IMA in predicting nephropathy. The area under curve (AUC) is 960 (95% CI 0.900:0.989) , p<0.0001, cutoff point>110.5 (senstivity=100%, specicity=94.4%, PPV=87.9% NPP=100%).

Discussion

IMA could be used to detect ischemia related to sub clinical vascular diseases in patients with Type 2DM.**(Dayanand et al., 2013).**In the present study most of the study participants (98.6%) were poorly controlled

diabetic patient, (With glycosylated hemoglobin >7%). Additionally, our study showed that the age of the participants did not affect the IMA levels and no significant difference between females and males' levels of IMA. There was significant correlation between the duration of diabetes mellitus and serum IMA, p <0.001 in agreement with **(Sowjanya et al., 2015; Saleh et al., 2019)**. On the other hand **(Chawla et al., 2016)** reported no correlation between serum IMA and the duration of DM ,their samples were taken from patients fasting overnight. In our study the patients with poor glycemic control (HbA1c ≥7%) had higher IMA levels than those with HbA1c<7% ,and the IMA showed a good correlation with HbA1c levels, these results agreed with **(Refaat et al., 2014)**. Similar observations have been reported by **(Piwowar et al., 2008)**.In this study the (UAC) ratio positively correlated with IMA, Agreed with**(KrzysekKorpacka et al., 2008 ;Ahmad et al., 2016)**,their research showed that the levels of IMA significantly correlated with the urinary albumin/creatinine ratio (P<0.001) and creatinine levels (P<0.05). This also agreed with **(Dahiya et al., 2013)**. Pearson's correlation analysis to creatinine and microalbuminuria with IMA, there was significant positive correlations of IMA with creatinine and with microalbuminuria (MA) this is supported by (**El Said et al., 2019)**.On the contrary **(Bilgi et al., 2017)**reported no correlation between albuminuria and creatinine and IMA in urine. **(El Said et al., 2019)** recommended the use of IMA as a marker of DN and glycemic state**.** The elevated levels of IMA could help in detecting subclinical diabetic vascular diseases**(Borderie et al., 2004; Dash et al., 2014).**Patients in group A were diagnosed with DN stage 3level of microalbuminuria (177.03±96.90) between (30-300mg)with high level of IMA(122.47±7.23).Inour study serum IMA was found to be able to detect DN by using ROC curve with (AUC 0.960), confidence interval(95%), , specificity (94.5%), sensitivity(100%) and p value< 0.001, this was agreed with **(Ahmed et al., 2016).**

Conclusion

The ischemia modified albumin levels were significantly higher and and showed positive correlation with duration of diabetes, random blood glucose, HbA1C, urinary microalbuminuria and urinary albumin creatinine ratio inT2DM with DN. Therefore, IMA could be used as a risk marker for Type 2 diabetes with diabetic nephropathy.

Study limitations

Our study had some limitations. Firstly, limited number of the participants. Secondly the need for follow up test of IMA levels could be better for patients 'evaluations.

Abbreviations

IMA; ischemia modified albumin, MA; microalbuminuria, UAC; urinary albumin creatinine ratio.

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

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, is prepared the idea of
the work and reviewed the statistics, formulated the results, wrote the discussion, and did the final edits, was responsible for writing discussion and statistics, Noreldin AK, 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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