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Research Article

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Serum Ischemia Modified Albumin as a Marker of Complications in Patients withType 2 DiabetesMellitus

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Abstract

Background : The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or absolute impairment in insulin secretion along with varying degrees of peripheral resistance to the action of insulin, Type 2 diabetes mellitus is by far the most common type of diabetes in adults (>90 percent), Diabetes is associated with complications such as cardiovascular diseases, retinopathy and neuropathy which can lead to chronic morbidities and mortality, Increased level of oxidative stress markers like malondialdehyde (MDA) has been detected in diabetes associated with complications. Ischemia modified albumin (IMA) is an altered type of serum albumin that forms under conditions of oxidative stress. Increased IMA has been described as a marker of ischemia reperfusion injury and dysfunction of endothelial L-arginine/nitric oxide pathway (affecting NO levels).

Aim of the work: To evaluate serum IMA among diabetic nephropathy, type 2 diabetes mellitus complications in comparison to healthy controls.

Results: The serum IMA were higher among group B than group A and group C with P value<0.005 which is statistically significant, there is positive predictive value of serum IMA to detect diabetic nephropathy and other diabetic complications.

Conclusion: There is positive predictive value of serum IMA to detect diabetic complications.

Keywords

Albumin; Diabetes mellitus

Abbrevations: ACS: Acute Coronary Syndrome; AOPP: Advanced Oxidation Protein Products; CRP: C-Reactive Protein; DM: Diabetes Mellitus; DN: Diabetic Nephropathy; DR: Diabetic Retinopathy

Introduction

In vivo studies showed that the molecule of albumin changes the ability of the first three amino acids N-Asp-Ala-His to bind free metal ions as cobalt, copper and nickel after modifications in hypoxia conditions [1], the ischemia-modified albumin (IMA) is a novel ischemia marker developed by quantifying the decrease in the metal binding capacity of albumin [2], Although the definitive and precise mechanism for IMA production *in vivo* is unknown as yet, it appears to be related to the generation of ROS that modifies metal binding domains of albumin. Both indirect and direct evidence supports this concept, Cobalt chloride is a well-established chemical inducer of hypoxia-like responses, such as erythropoiesis and angiogenesis *in vivo*, likely involving an increased DNA binding activity of hypoxia-inducible factor-1α (HIF-1α) to its target genomic sequences, It has been speculated that cobalt might stabilize HIF-1α through generation of ROS by a nonenzymatic, mitochondrial mechanism. Under normoxic conditions, the main mediator HIF-1α is rapidly degraded by the proteasome [3].

Reference values

Reference values of IMA were determined from a population of 283 healthy individuals and ranged from 52 to 116 kilounits/L, with a 95th percentile at 85 kilounits/L (Cobas Mira) [4], after multivariate analysis, results of some studies IMA levels>85 U/ml suggested myocardial ischemia [5].

Relation to albumin

In particular study, a significant inverse association was observed between IMA and serum albumin, accordingly, it has been suggested that IMA serum concentrations in patients with extremely low or high serum albumin levels (<20 or >55 g/L) may be unreliable and lacking in clinically informative value [6].

Normal values

While the optimum cut-off for IMA for ruling out ACS is 85 kilounits/L, the manufacturer has suggested a higher value of 100 kilounits/L for risk stratification. IMA is normally distributed in a group of apparently healthy volunteers and is not correlated with smoking, age, race, gender, or Framingham risk score [7].

Importance of ischemia modified albumin

In clinical and experimental studies conducted so far, it has been demonstrated that IMA elevates depending on oxidative stress after acute ischemia and returns to normal levels in hours after reperfusions [8], In the body, IMA formation occurs not only acutely but also due to the chronic oxidative damage [9].

It has been proposed by various authors that IMA increases wherever the albumin passes through ischemic tissues, Hence, though approved as a marker in cardiac ischemia, now it is being studied in context of other diseases where there is a prevalence of increased oxidative stress and ischemia, like diabetes mellitus, liver diseases, obese post-menopausal women, complicated pregnancies and cancers [10].

Role of ischemia modified albumin in diagnosis of diabetes mellitus and diabetic complications

Hyperglycaemia in Type 2 Diabetes mellitus has been implicated in the pathogenesis and progression of the disease process with

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microvascular complications as per various researches [11]. Hyperglycaemia and inflammation reduces the capacity of albumin to bind cobalt, resulting in higher IMA levels [12], in published studies, formation of IMA appears to be involved in the initial stage of development of atheromatous plaques, and may be associated with early assessment of overall patient risks [13], Correlations between the modified albumin and HbA1c and homocysteine were described [14], IMA may not be specific applicable to be a marker for the detection of endothelial ischemic damage in diabetic patients who are already at a high risk for cardiovascular disease, Significance of IMA to those metabolic parameters might reflect a chronic production of ROS, but on the other hand, there is a concern that the increased IMA was a response to other factors such as glycation of albumin by chronic hyperglycemia [15], Plasma IMA levels are reported to correlate with parameters of oxidative stress like Advanced Oxidation Protein Products [AOPP] and thiol groups [16], Higher levels of IMA and CRP were detected in patients with T2 DM and T2 DKA [17]. There had been various studies performed on diabetic complications and serum IMA levels and close relationship has been determined [18], Hyperglycaemia-induced ischemia, inflammation, and oxidative stress might increase the levels of IMA in the serum and also in the kidney, resulting in podocyte malfunction, their excess accumulation along the extracellular matrix in the glomerulus and tubulointerstitium leads to vascular endothelial damage in diabetes [19,20].

Patients, materials and methods

Population of study and disease condition: Patients with type 2 DM with and without nephropathy.

Inclusion criteria: Patients with type 2 DM.

Exclusion criteria: Patients with type I DM, gestational DM, patients with other diseases of the kidney not related to DN, Patients with coronary heart disease.

Methodology in details

A total of 62 patients with type 2 diabetes mellitus who attended the outpatient clinic of the Department of Internal Medicine, Kasr Al Aini Hospital, Cairo University, and 29 healthy age-matched control individuals were included in the study. The study was performed from December 2015 to December 2016. Participants were subdivided into three groups: Group A: 33 type 2 DM patients without nephropathy, Group B: 29 type 2 DM patients with nephropathy and Group C: 29 healthy subjects as control.

Ethical aspects

Research protocols were approved by the medical ethics committee of Kasr al Aini Medical School, Cairo University. All participants provided a written informed consent after the research protocols were explained carefully to them. Informed consent was obtained from all the study participants and their approval was taken by signature.

For each subject the following were done

-History taking, detailed physical examination, Measurement of weight, height and calculation of BMI (Wt(kg)/height^2(m^2), ECG to exclude coronary ischemia, Fundus examination, Abdominal ultrasound, Laboratory investigations in the form of Fasting and postprandial blood glucose, Lipid profile in the form of serum cholesterol, serum triglycerides, serum LDL, serum HDL, Serum creatinine. Urinary albumin/creatinine ratio. Urinary albumin were measured using immunoturbidmetric method and urinary creatinine was measured using Jaffe reaction) and Urinary albumin/creatinine ratio was calculated [21]. Serum ischemia modified albumin which was measured by colorimetric method [22]. All routine investigations were determined on auto-analyzer using colorimetric methods. The determination of fasting blood glucose, post prandial blood glucose, serum creatinine and lipid profile were carried out on Dimension RxL Max analyzer (Siemens Healthcare GmbH Henkestr. 127, 91052 Erlangen, Germany) by colorimetric techniques. HbA_1c was determined using cation exchange resin. Albumin concentrations were measured in urine using a Mininephe microalbumin kit based on nephlometry method on Mininephelometer (AD200) (The Binding Site, Birmingham, UK) [23]. Urinary creatinine was determined on Dimension RxL Max analyzer by colorimetric technique and the ratio of urine albumin to creatinine was used to define microalbuminuria.

IMA determination

Sample collection: Two ml of venous blood samples were collected from each subject participating in the study and was left to clot then the serum was separated by centrifugation at 3000 xg for 10 minutes and IMA assay was performed immediately.

Principle and assay procedure: IMA concentration was determined by addition of a known amount of cobalt (2) to a serum sample and measurement of the unbound cobalt (2) by the intensity of colored complex formed after reacting with dithiothreitol (DTT) by colorimeter. An inverse relationship thus exists between the level of albumin bound cobalt and the intensity of the color formed. The preparations for the Co (2) albumin binding protocol involved the addition of 200 µL of patient serum to 50 µl of a solution of 1 g/1 cobalt chloride, followed by vigorous mixing and 10-min incubation. Dithiothreitol (50 µl of a 1.5 g/1 solution) was then added and mixed. After 2-min incubation, 1.0 ml of a 9.0 g/1 solution of NaCl were added. The absorbance of the assay mixture was read at 470 nm, the blank was prepared similarly with the exclusion of DTT. The values are expressed in U/ml, standard curve was prepared in the range 6.0-60.0 µg $CoCl_2$/ml. One IMA unit was defined as µg of free Co (2) in the reaction mixture per ml of serum sample [24].

Statistical analysis

Data were collected, tabulated then statistically analyzed using the Statistical Package for Social Sciences (SPSS) computer software version 20.0 (IBM, Armonk, NY, USA). Numerical variables were presented as mean and standard deviation (± SD), while categorical variables were presented as number and percentage. *Chi*-square test (χ^2) was used for comparison between groups as regard qualitative demographic data and score variables. Independent *t*-test and One-way ANOVA with LSD post-hoc tests were used for comparison and multiple comparisons between groups as regard quantitative variables. A difference with a *P* value ≤0.05 was considered statistically significant.

Results

The results were divided into three groups group A which consists of patients diagnosed with diabetes mellitus which included 33 patients aged from 50 to 55 years old, with 18 males and 15 females, 16 of them treated with insulin and 17 of them treated by oral hypoglycemic drugs, no one of them had diabetic peripheral neuropathy in general examinations, no one of them showed diabetic retinopathy by fundus examinations, group B included 29 patients

of the same age consists of 15 males, 14 females, 20 patients treated with insulin, 9 patients treated with oral hypoglycemic drugs, with 25 patients diagnosed with diabetic peripheral neuropathy with general examinations, 25 patients were diagnosed with diabetic retinopathy by fundus examinations, 20 patients were diagnosed with fatty liver by abdominal ultrasound, and group C included 29 healthy control subjects. On comparison of group B with group A, the number of patients diagnosed with diabetic neuropathy by general examination, and those with diabetic retinopathy by fundus examination, and the number of patients diagnosed by fatty liver by abdominal ultrasound in group B were higher than those in group A with P values<0.05 which were statistically significant, the values of systolic, diastolic blood pressure, HbA1C, UAC ratio, serum creatinine, and serum IMA were higher in group B than those in group A with P values<0.001 which is statistically significant, while on comparison between group A and group C no significant difference was found between group A and control subjects regarding presence of neuropathy, retinopathy or fatty liver, the value of BMI, systolic, diastolic blood pressure, serum glucose (fasting and postprandial), HbA1c, lipid profile except HDL, UAC ratio, and serum IMA were higher in patients with group A than those in healthy controls (group C) with p value<0.001 which is statistically significant, serum HDL-c is statistically significantly higher in control subjects than patients with group A, while on comparison between B and C, the frequency of diabetic neuropathy, diabetic retinopathy by fundus examinations, fatty liver by abdominal ultrasound were higher in group B than those in healthy control (group C) with P values<0.001 which were statistically significant, the values of BMI, systolic, diastolic blood pressure, fasting, postprandial blood glucose, HbA1C, Lipid profiles except HDL, Serum creatinine, UAC ratio, and serum IMA were higher in group B than those in healthy control (group C) with P value<0.001 which is statistically significant, While HDL-c is significantly lower in group B, on correlating serum IMA and various parameters in the study there is statistically significant positive correlation between serum IMA and duration of diabetes mellitus, systolic and diastolic blood pressure, FBG, PPBG, serum cholesterol, LDL c, TG, UACR, serum creatinine, and statistically significant negative correlation between serum IMA and HDL, while on correlating serum IMA to HbA1c receiver operating characteristic curve analysis in (Figure 1) showing a positive correlations between serum IMA and HbA1C with p<0.005, r=0.795 which is statistically significant, while on correlating serum IMA to serum fasting blood glucose receiver operating characteristic curve analysis (Figure 2) showing that serum fasting blood glucose is positively correlated with serum IMA with P value<0.005 and r=0.709 which is statistically significant, while on correlating serum IMA to serum postprandial blood glucose receiver operator characteristic curve analysis in (Figure 3) showing that serum postprandial blood glucose is positively correlated with serum IMA with P value<0.005, r=0.747, which is statistically significant, while on correlating serum IMA to lipid profile as cholesterol receiver operating characteristics curve analysis in (Figure 4) showed a significant correlation between serum cholesterol and serum IMA with P value<0.005, r=0.794 which is statistically significant while on correlating serum IMA to serum triglycerides receiver operating characteristic curve analysis in (Figure 5) showed significant positive correlation between serum triglycerides and serum IMA with P value<0.005 and r=0.515 which is statistically significant while on correlating serum IMA to serum LDL in (Figure 6) receiver operating characteristic curve analysis showed significant correlation between serum LDL and serum IMA with P value<0.005, r=0.646 which is statistically significant, while on correlating serum IMA to serum HDL receiver operating characteristic curve analysis in (Figure 7) showing negative correlation between serum HDL and serum IMA with P value<0.6 and r=-0.5 which is statistically significant, while on correlating serum IMA to urine albumin creatinine ratio receiver operating characteristic curve analysis in (Figure 8) showing positive correlation between UAC ratio and serum IMA with P value<0.005 and r=0.734 which is statistically significant, and when correlating serum IMA to serum creatinine receiver operating characteristic curve analysis in (Figure 9) showing positive correlation between serum creatinine and serum IMA with P value<0.005, r=0.765 which is statistically significant, The values of serum IMA among different groups showed that value of serum IMA

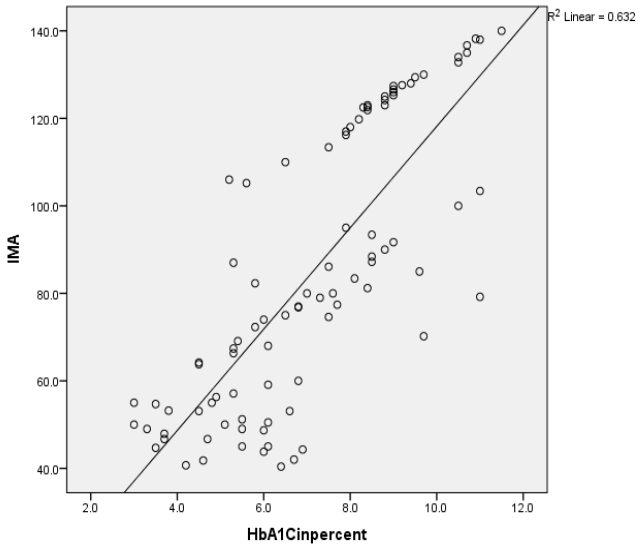

Figure 1: Receiver operating characteristic curve analysis showing a positive correlations between serum IMA and HbA1C with p<0.005, r=0.795 which is statistically significant.

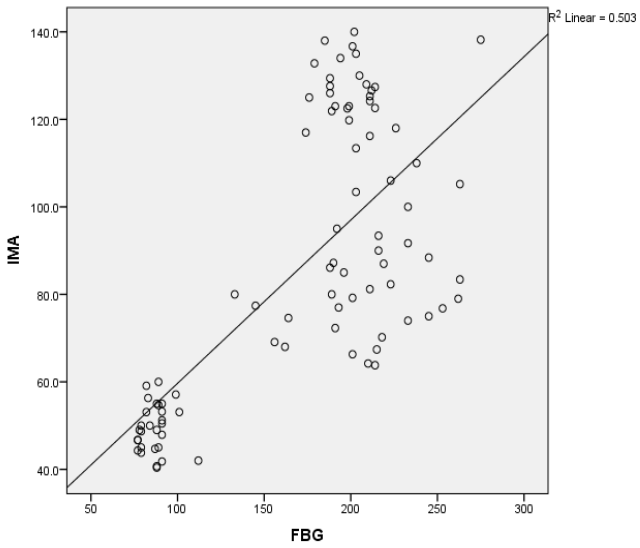

Figure 2: Receiver operating characteristic curve analysis showing that serum fasting blood glucose is positively correlated with serum IMA with P value <0.005 and r=0.709 which is statistically significant.

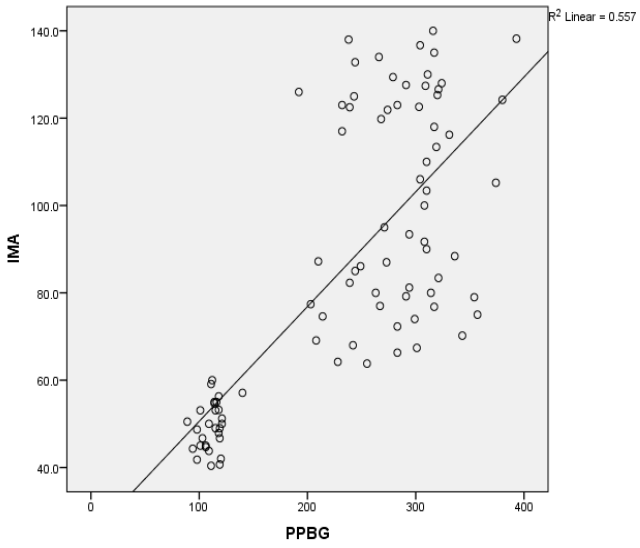

Figure 3: Receiver operator characteristic curve analysis showing that serum postprandial blood glucose is positively correlated with serum IMA with P value<0.005 , r=0.747 , which is statistically significant.

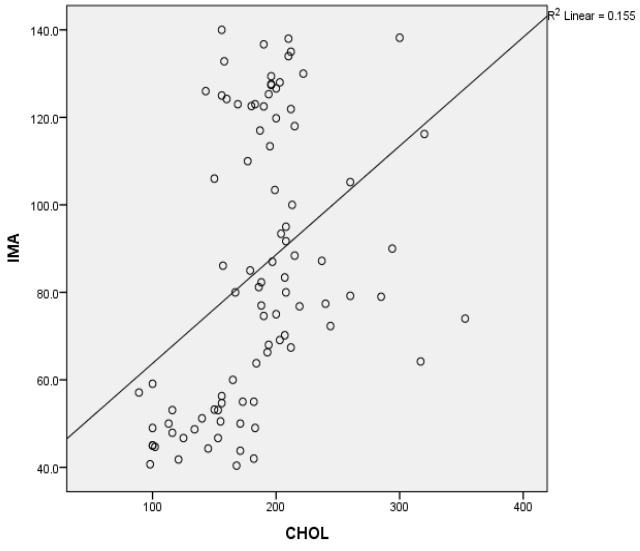

Figure 4: Receiver operating characteristics curve analysis showed a significant correlation between serum cholesterol and serum IMA with P value<0.005 , r=0.794 which is statistically significant.

among patients with diabetic nephropathy (group B) were higher than that their values in diabetic patients without nephropathy (group A) that were higher than their values in healthy controls (group C) with p value<0.001 which is statistically significant, so there is strong positive correlation between serum IMA and diabetic nephropathy also (Figure 10) showing the mean value of serum IMA in group B (diabetic nephropathy) were higher than their values in group A and group C, the value of serum IMA among those with peripheral diabetic neuropathy (108.899 U/ml) were higher than their value among those with no peripheral diabetic neuropathy (82.899 U/ml) with P value 0.024 which is statistically significant, so there is positive correlation between serum IMA and diabetic peripheral neuropathy, the ability of serum IMA to predict diabetic peripheral neuropathy with AUC 0.722, 95%C.I 0.583-0.861 with P value 0.039 which is statistically significant, and with cut-off 89.2 with sensitivity 62.5 and specificity 62.7% (Figure 11), the value of serum IMA among those with diabetic retinopathy patients were higher than their values in patients without diabetic retinopathy with P value<0.001 so there is significant correlation between serum IMA and diabetic retinopathy, The mean values of serum IMA among patients with fatty liver

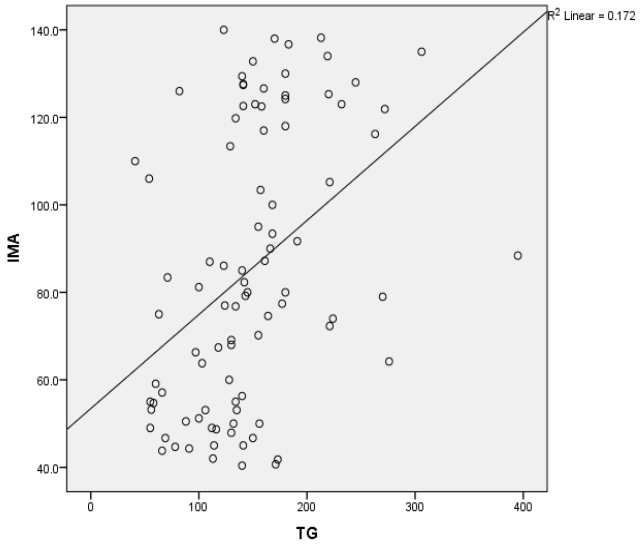

Figure 5: Receiver operating characteristic curve analysis showed significant positive correlation between serum triglycerides and serum IMA with P value<0.005 and r=0.515 which is statistically significant.

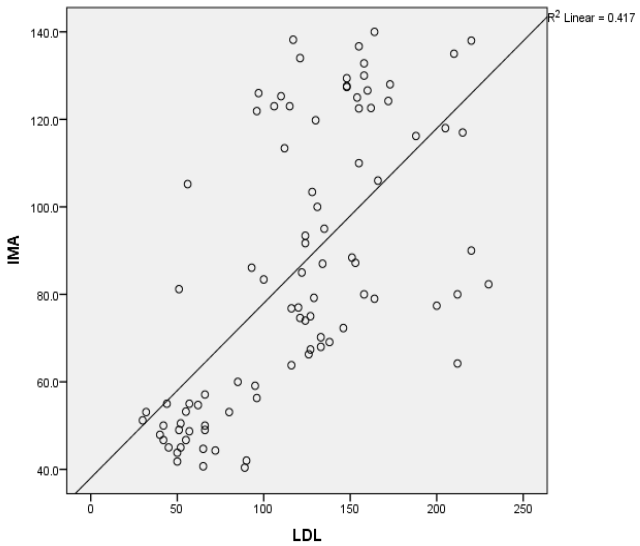

Figure 6: Receiver operating characteristic curve analysis showed significant positive correlation between serum triglycerides and serum IMA with P value<0.005 and r=0.515 which is statistically significant.

disease by abdominal ultrasound were higher than their values among patients without fatty liver disease by abdominal ultrasounds with (Figure 12) P value<0.001 which is statistically significant, so there is strong positive correlation between serum IMA and fatty liver as a complication of DM, the ability of serum IMA to predict fatty liver with AUC 0.820, 95%C.I 0.726-0.914 with P value<0.001 with sensitivity 72.7 % and specificity 74.5%., significant difference of serum IMA in group B than that of group A and group C with P value<0.001 which is statistically significant, a moderate positive correlation exists between IMA and creatinine in the whole sample

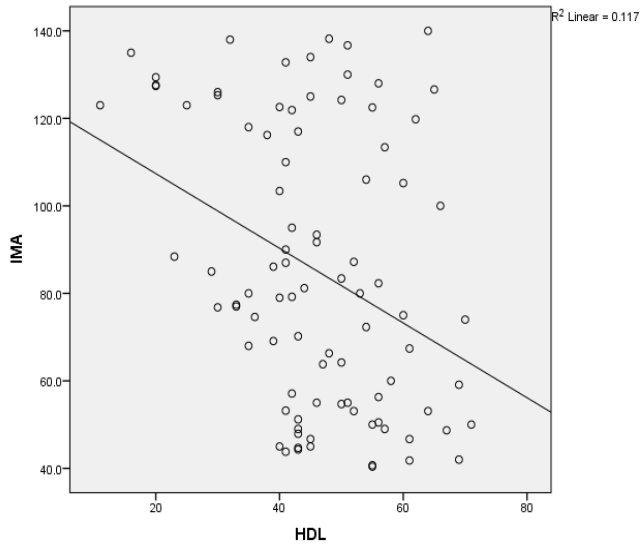

Figure 7: Receiver operating characteristic curve analysis showing negative correlation between serum HDL and serum IMA with P value<0.6 and r=-0.5 which is statistically significant.

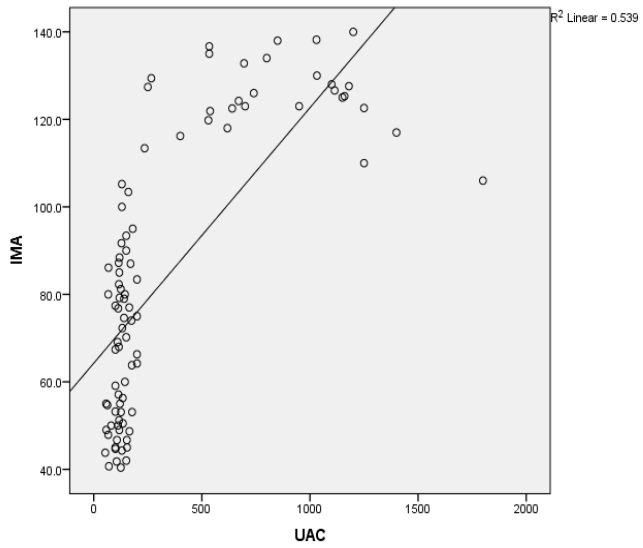

Figure 8: Receiver operating characteristics curve analysis showing positive correlation between UAC ratio and serum IMA with P value<0.005 and r=0.734 which is statistically significant.

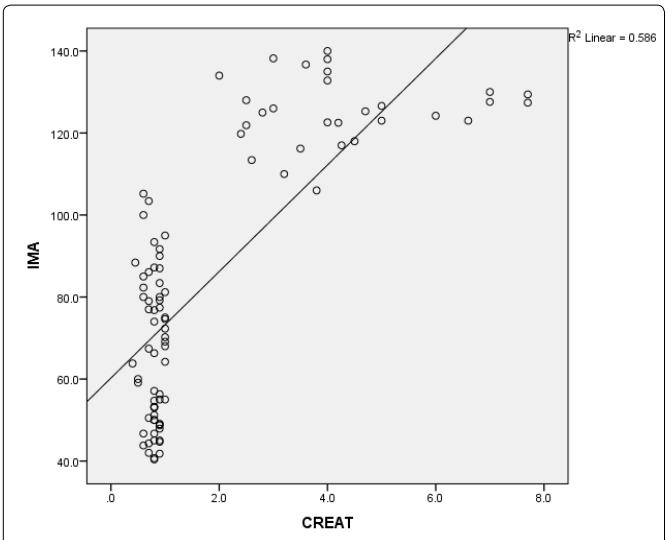

Figure 9: Receiver operating characteristic curve analysis showing positive correlation between serum creatinine and serum IMA with P value<0.005, r=0.765 which is statistically significant.

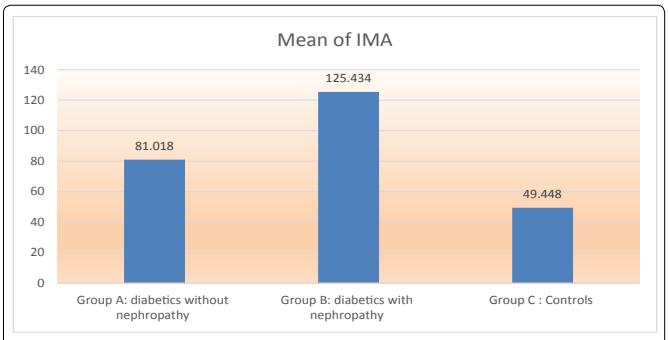

Figure 10: Receiver operating characteristic curve analysis showing positive correlation between serum creatinine and serum IMA with P value<0.005, r=0.765 which is statistically significant.

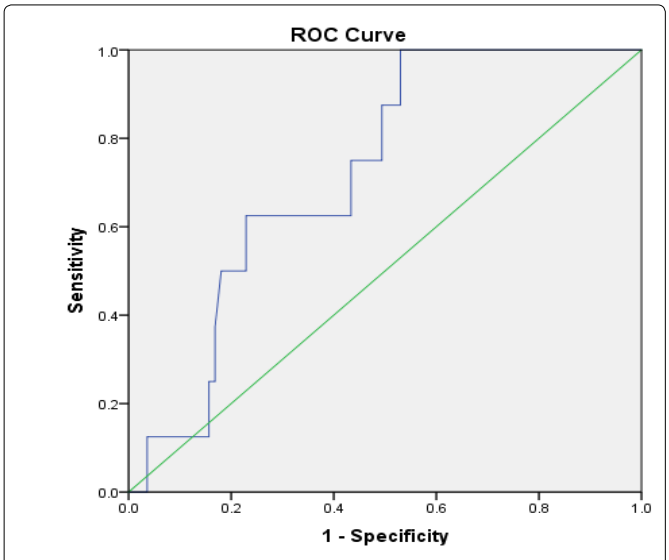

Figure 11: ROC for PN.

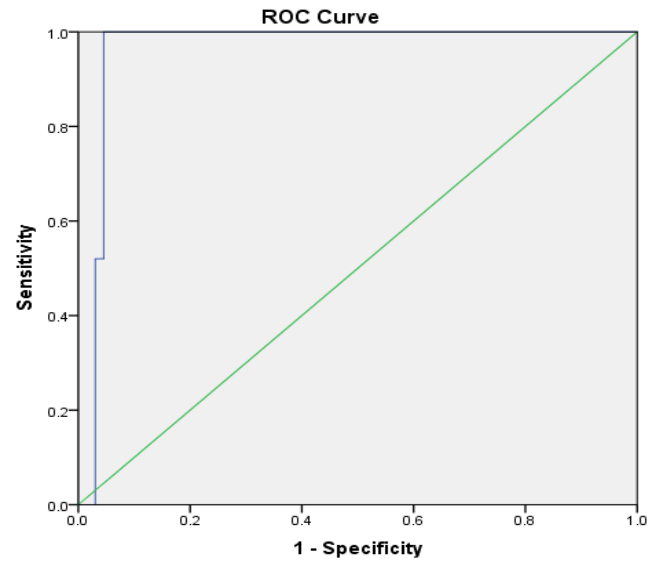

Figure 12: ROC for DR.

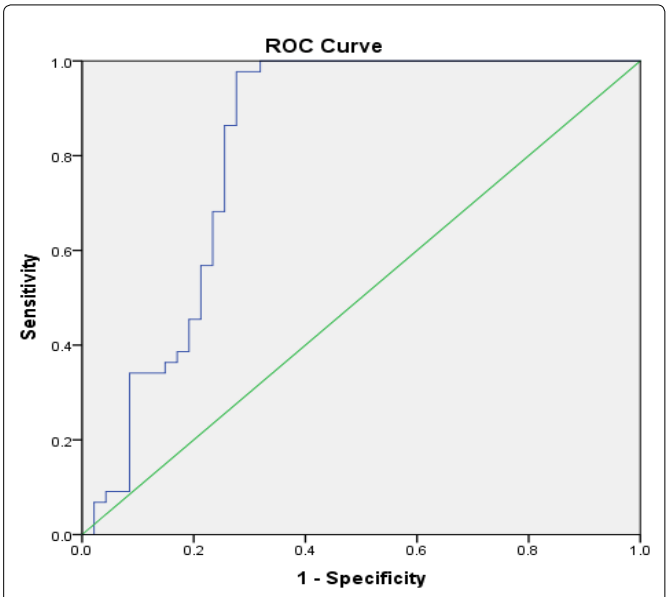

Figure 13: ROC for fatty liver.

R=0.765 and P<0.001, and the ability of serum (Figures 13 and 14) IMA in detecting diabetic nephropathy has 100% specificity, and 100% sensitivity (Tables 1-18).

Discussion

Our case control study included 91 patients, 33 patients with diabetes mellitus type 2, 29 patients with diabetic nephropathy complicating type 2 diabetes mellitus, and 29 healthy controls, The aim of the study was to evaluate IMA in type 2 diabetic patients with various complications, Significant difference was observed between mean duration of disease in group B than that in group A with p value<0.092 which is statistically significant, while HbA1c as a marker of glycemic control was statistically significantly higher in group B patients with diabetic nephropathy than those of group A without nephropathy, this could reflect the association between poor glycemic control and duration of DM and development of diabetic complications as nephropathy this was supported and agreed by Kaefer et al. [12,25-27].

On correlation between serum IMA and duration of diabetes mellitus among populations of study, it showed positive correlation between serum IMA, and duration of diabetes mellitus with p value<0.056, r=0.244 which is statistically significant which is agreed and supported by Sowjanya et al. [25]. The correlations between serum IMA and different parameters of glucose control as HbA1c, FBG, PPBG showed positive correlation between them with p value<0.05 which is statistically significant these results were supported and agreed by Chawla et al. [26]. Serum level of IMA was positively correlated with HbA1c, a marker of glycaemic control and an indicator of development of complications, This finding is supported by Sowjanya who reported that the positive association of raised plasma IMA with HbA1c may be an effect of increased oxidative stress and free radical generation leading to widespread inflammation of vascular endothelium et al. [25-27], the resultant tissue hypoxia might have contributed to the increased modification of albumin attributing towards raised IMA level. The correlations between serum IMA and lipid profiles shows positive correlation between elevated serum cholesterol, serum triglycerides, and serum LDL, with serum IMA in the whole population of study and negative correlation between serum IMA and HDL these results were supported by Refaat et al. [28], There is significant difference between BMI in group B than that in group C, and there is significant difference between BMI in group A than that in group C with P value<0.001 which is statistically significant this was supported and agreed by Arslan et al. [29], In our study IMA and BMI were positively correlated (p-value<0.003) this was in agreement with Joha et al. [30], who found a positive correlation between serum ischemia modified albumin and BMI in obese patients above 30 kg/m^2 and with Arslan et al. [29] study which positively correlated serum ischemia modified albumin with obesity and metabolic syndrome, on the contrary Yigitbasi et al. [31], found no significant correlation between ischemia modified albumin and BMI. Significant difference in UAC was observed between group B

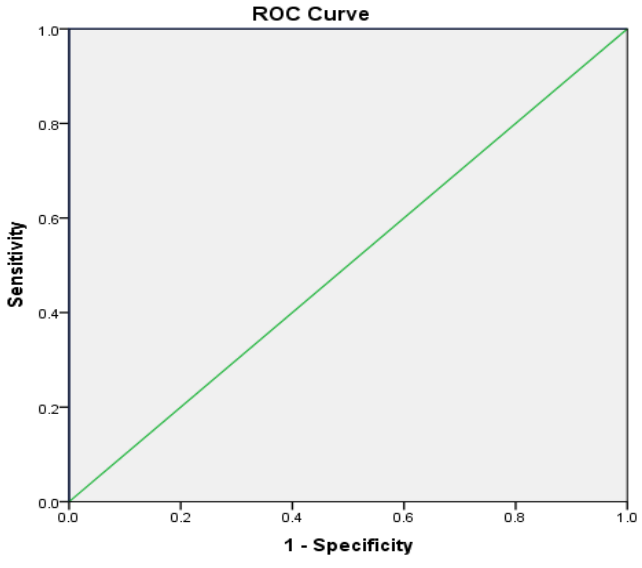

Figure 14: ROC of diabetic nephropathy.

Table 1: Comparison of the studied groups.

Item	Group A N=33		Group B N=29		Group C N=29	
	Frequency	%	Frequency	%	Frequency	%
Sex						
Male	18	54.5%	15	51.7%	15	51.7%
Female	15	45.45%	14	48.27%	14	48.27%
Treatment						
Insulin	16	48.48%	20	68.9%	-----	---
Oral hypoglycemic drugs	17	51.51%	9	31.03%	-----	----
PN						
Negative	33	100%	4	13.7%	29	100%
Positive			25	86.2%		
DR						
Negative	33	100%	4	13.7%	29	100%
Positive			25	86.2%		
U/S						
Normal	33	100%	9	31.03%	29	100%
F.I.			20	68.9%		

DR: Diabetic Nephropathy; F.L: Fatty Liver; N: Number of Patients; PR: Peripheral Neuropathy; U/S: Abdominal Ultrasound.

Table 2: Demographic, clinical and laboratory data of the studied groups.

Item	Group A N=33	Group B N=29	Group C N=29
	Mean ± SD	Mean ± SD	Mean ± SD
Age in years	51.9 ± 6.545	50.5 ± 5.56	51.5 ± 4.5
Duration in years	8.66 ± 4.80	11.18 ± 6.526	-----
BMI	27.39 ± 3.992	27.93 ± 4.317	24.48 ± 2.148
BP systolic	130.61 ± 10.589	147.59 ± 8.724	118.97 ± 3.099
BP Diastolic	86.97 ± 5.855	91.38 ± 4.411	78.62 ± 5.158
HbA1C in percent	7.388 ± 1.798	8.990 ± 1.3857	4.028 ± 1.2265
FBG	203.66 ± 20.274	208.36 ± 32.951	86.90 ± 7.993
PPBG	283.73 ± 45.229	291.72 ± 44.524	111.55 ± 10.284
CHOL	195.86 ± 28.150	218.267 ± 43.046	138.52 ± 30.264
TG	161.27 ± 64.456	170.66 ± 60.309	108.03 ± 36.954
LDL	138 ± 40.464	152.34 ± 34.52	60.38 ± 18.204
HDL	44.97 ± 10.987	40.93 ± 14.919	52.48 ± 9.661
UAC	13.5 ± 5.5	848 ± 379.043	11.6 ± 3.4
IMA	81.018 ± 10.9490	125.434 ± 8.4077	49.448 ± 5.5295
CREAT	0.808 ± 0.1733	4.295 ± 1.6258	0.793 ± 0.1223

BMI: Body Mass Index; BP: Blood Pressure; Chol: Serum Cholesterol; CREAT: Serum Creatinine; FBG: Fasting Blood Glucose; Hba1c: Glycated Hemoglobin; HDL: Serum High Density Lipoprotein; IMA: Serum Ischemia Modified Albumin; LDL: Serum Low Density Lipoprotein; PPBG: Postprandial Blood Glucose; SD: Standard Deviation; TG: Serum Triglycerides;

UAC: Urinary Albumin Creatinine Ratio

Table 3: Comparison between groups A and B regarding the enlisted variables.

Item	Group A N=33		Group B N=29		P Value
	Frequency	%	Frequency	%	
Sex					
Male	18	54.54%	15	51.7%	0.78
Female	15	45.45%	14	48.27%	
Treatment					
Insulin	16	48.48%	20	68.9%	<0.001*
Oral hypoglycemic drugs	17	58.6%	9	31.03%	
PN					
Negative	33	100%	4	13.7%	<0.001*
Positive			25	86.2%	

DR					
Negative	33	100%	4	13.7%	<0.001*
Positive			25	86.2%	
U/S					
Normal	33	100%	9	31.03%	<0.001
F.I.			20	68.9%	
The number of patients diagnosed with diabetic neuropathy by general examination , and those with diabetic retinopathy by fundus examination ,and the number of patients diagnosed by fatty liver by abdominal ultrasound in group B were higher than those in group A with P values <0.05 which were statistically significant					

Table 4: Comparison between groups A and B regarding the enlisted variables.

Item	Group A N=33	Group B N=29	P value
	Mean ± SD	Mean ± SD	
Age in years	51.97 ± 6.545	50.5 ± 5.56	0.78
Duration in years	8.66 ± 4.80	11.18 ± 6.526	0.092
BMI	27.39 ± 3.992	27.93 ± 4.317	0.613
BP systolic	130.61 ± 10.589	147.59 ± 8.724	0.0001*
BP Diastolic	86.97 ± 5.855	91.38 ± 4.411	0.002*
HbA1Cinpercent	7.388 ± 1.7980	8.990 ± 1.3857	0.0001*
FBG	203.66 ± 20.247	208.36 ± 32.951	0.508
PPBG	283.73 ± 45.229	291.72 ± 44.524	0.487
CHOL	195.86 ± 28.150	218.267 ± 43.046	0.032*
TG	161.27 ± 64.546	170.66 ± 60.309	0.558
LDL	138 ± 40.464	152.34 ± 34.4452	0.141
HDL	44.97 ± 10.987	40.93 ± 14.919	0.226
UAC	13.5 ± 5.5	848.83 ± 379.043	<0.001*
IMA	81.018 ± 10.9490	125.434 ± 8.4077	<0.001*
CREAT	0.808 ± 0.1733	4.295 ± 1.6258	<0.001*
The values of systolic , diastolic blood pressure , HbA1C , UAC ratio , serum creatinine , and serum IMA were higher in group B than those in group A with P values <0.001 which is statistically significant.			

Table 5: Comparison between groups A and C regarding the enlisted variables.

Item	Group A N=33		Group C N=29		P value
	Frequency	%	Frequency	%	
Sex					
Male	18	54.54%	15	51.7%	0.9
Female	15	51.7%	14	48.27%	
Treatment					
Insulin	16	48.48%	------	----	a
Oral hypoglycemic drugs	17	51.51%	------	-----	
PN					
Negative	33	100%	29	100%	0.99
Positive					
DR					
Negative	33	100%	29	100%	0.99
Positive					
U/S					
Normal	33	100%	29	100%	0.99
F.I.					
a: undetermined.. no significant difference was found between group A and control subjects regarding presence of neuropathy , retinopathy or fatty liver					

Table 6: Comparison between groups A and C regarding the enlisted variables.

Item	Group A N=33	Group C N=29	P value
	Mean ± SD	Mean ± SD	
Age in years	51.97 ± 6.545	50.5 ± 5.56	0.78
Duration in years	8.66 ± 4.80	11.18 ± 6.526	0.092
BMI	27.39 ± 3.992	27.93 ± 4.317	0.613
BP systolic	130.61 ± 10.589	147.59 ± 8.724	0.0001*
BP diastolic	86.97 ± 5.855	91.38 ± 4.411	0.002*
HbA1Cinpercent	7.388 ± 1.7980	8.990 ± 1.3857	0.0001*
FBG	203.66 ± 20.247	208.36 ± 32.951	0.508
PPBG	283.73 ± 45.229	291.72 ± 44.524	0.487
CHOL	195.86 ± 28.150	218.267 ± 43.046	0.032*
TG	161.27 ± 64.546	170.66 ± 60.309	0.558
LDL	138 ± 40.464	152.34 ± 34.4452	0.141
HDL	44.97 ± 10.987	40.93 ± 14.919	0.226
UAC	13.5 ± 5.5	848.83 ± 379.043	<0.001*
IMA	81.018 ± 10.9490	125.434 ± 8.4077	<0.001*
CREAT	0.808 ± 0.1733	4.295 ± 1.6258	<0.001*
The value of BMI , systolic , diastolic blood pressure , serum glucose (fasting and postprandial) , HbA1c , lipid profile except HDL , UAC ratio , and serum IMA were higher in patients with group A than those in healthy controls (group C) with p value <0.001 which is statistically significant, serum HDL-c is statistically significantly higher in control subjects than patients with group A			

Table 7: Comparison between groups B and C regarding the enlisted variables.

Item	Group B N=29		Group C N=29		P value
	Frequency	%	Frequency	%	
Sex					
Male	15	51.7%	15	51.7%	0.99
Female	14	48.2%	14	48.27%	
Treatment					
Insulin	20	68.9%	-----		undetermined
Oral hypoglycemic drugs	9	31.03%	-----		
PN					
Negative	4	13.7%	29	100%	0.0001*
Positive	25	86.2%			
DR					
Negative	4	13.7%	29	100	0.0001*
Positive	25	86.2%			
U/S					
Normal	9	31.03%	29	100	0.0001*
F.I.	20	68.96%		0	
The frequency of diabetic neuropathy , diabetic retinopathy by fundus examinations , fatty liver by abdominal ultrasound were higher in group B than those in healthy control (group C) with P values <0.001 which were statistically significant.					

Table 8: Comparison between groups B and C regarding the enlisted variables.

Item	Group B	Group C N=29	P value
	Mean ± SD	Mean ± SD	
Age in years	50.5 ± 5.56	51.5 ± 4.5	0.69
Duration in years	11.18 ± 6.526	0a	0.0001*
BMI	27.93 ± 4.317	24.48 ± 2.148	0.0001*
BP systolic	147.59 ± 8.742	118.97 ± 3.099	0.0001*
BP Diastolic	91.38 ± 4.411	78.62 ± 5.1585	0.0001*
HbA1Cinpercent	8.990 ± 1.3857	4.028 ± 1.2265	0.0001*
FBG	208.36 ± 32.951	86.90 ± 7.993	0.0001*
PPBG	291.72 ± 44.524	111.55 ± 10.284	0.0001*
CHOL	218.267 ± 43.046	138.52 ± 30.264	0.0001*
TG	170.66 ± 60.309	108.03 ± 36.954	0.0001*

LDL	152.34 ± 34.452	60.38 ± 18.204	0.0001*
HDL	40.93 ± 14.919	52.48 ± 9.661	0.001*
UAC	848.83 ± 379.043	11.6 ± 3.4	0.0001*
IMA	125.434 ± 8.4077	49.448 ± 5.5295	0.0001*
CREAT	4.295 ± 1.6258	0.793 ± 0.1223	0.0001*
The values of BMI , systolic , diastolic blood pressure , fasting , postprandial blood glucose , HbA1C , Lipid profiles except HDL , Serum creatinine , UAC ratio , and serum IMA were higher in group B than those in healthy control (Group C) with P value <0.001 which is statistically significant, While HDL-c is significantly lower in group B.			

Table 9: Correlation between serum IMA and different variables.

Correlation between Serum ischemia modified albumin and different variables as a whole (Serum IMA)		
	P value	**R**
Variable		
Age in years	0.101	0.173
Duration of DM	0.056*	0.244
BMI	0.003*	0.706
B.P systolic	0.0001*	0.776
B.P diastolic	0.0001*	0.631
HbA1c	0.0001*	0.795
F.B.G	0.0001*	0.709
P.P.B.G	0.0001*	0.747
Cholesterol	0.0001*	0.794
TG	0.0001*	0.515
LDL	0.0001*	0.646
HDL	0.6	-0.5
UAC ratio	0.0001*	0.734
Serum creatinine	0.0001*	0.765
P value <0.005 is significant statistically, R explanation 1-Positive or negative according to the sign 2-<0.5 weak correlation 3-Between 0.5-0.7 moderate correlation 4->0.7 strong correlation 5-As shown in this table there is statistically significant positive correlation between serum IMA and duration of diabetes mellitus , systolic and diastolic blood pressure , FBG, PPBG, serum cholesterol , LDL –c , TG , UACR, serum creatinine , and statistically significant negative correlation between serum IMA and HDL.		

Table 10: IMA among different study groups.

IMA				
	N	Mean	Std. Deviation	P value
Group A: diabetics without nephropathy (63.8-105.2 U/ml)	33	81.018	10.9490	<0.001*
Group B: diabetics with nephropathy (106-140 U/ml)	29	125.434	8.4077	
Group C: Controls (40-60 U/ml)	29	49.448	5.5295	
Total	91	85.112	31.8435	
The values of serum IMA among different groups showed that value of serum IMA among patients with diabetic nephropathy (group B) were higher than that their values in diabetic patients without nephropathy (group A) that were higher than their values in healthy controls (group C) with p value <0.001 which is statistically significant, so there is strong positive correlation between serum IMA and diabetic nephropathy				

Table 11: IMA among different nerve status either diabetic peripheral neuropathy or normal nerves.

Group Statistics					
	PN	N	Mean	Std. Deviation	
IMA	Negative	66	82.899	31.6980	0.024*
	Positive	25	108.075	24.6273	
The value of serum IMA among those with peripheral diabetic neuropathy (108.899 U/ml) were higher than their value among those with no peripheral diabetic neuropathy (82.899 U/ ml) with P value 0.024 which is statistically significant, so there is positive correlation between serum IMA and diabetic peripheral neuropathy.					

Table 12: Ability of IMA to predict PN.

	AUC*	**95% CI**	**P value**	**Cut-Off**	**Sensitivity**	**Specificity**
IMA	0.722	0.583– 0.861	**0.039***	89.2	62.5%	62.7%
The ability of serum IMA to predict diabetic peripheral neuropathy with AUC 0.722, 95%C.I 0.583-0.861 with P value 0.039 which is statistically significant , and with cut-off 89.2 with sensitivity 62.5 and specificity 62.7.						

Table 13: IMA among different status of the retina either diabetic retinopathy or normal retina.

Group Statistics					
	DR	**N**	**Mean**	**Std. Deviation**	**P value**
IMA	Negative	66	69.952	23.1448	<0.001*
	Positive	25	125.136	7.1417	
The value of serum IMA among those with diabetic retinopathy patients were higher than their values in patients without diabetic retinopathy with P value <0.001 so there is significant correlation between serum IMA and diabetic retinopathy.					

Table 14: Ability of IMA to predict DR.

	AUC*	**95% CI**	**P value**	**Cut-Off**	**Sensitivity**	**Specificity**
IMA	0.962	0.919– 1.000	**<0.001***	111.7	96.0%	95.5%
The ability of serum IMA to predict diabetic retinopathy with AUC 0.962 , 95%C.I 0.919-1.00, with P value <0.001 , and cut-off 111.7 with sensitivity 96% and specificity 95.5.						

Table 15: IMA among different abdominal ultrasound either in fatty liver or normal liver.

Group statistics					
	US	**N**	**Mean**	**Std. Deviation**	**P value**
IMA	Normal	71	69.357	31.0556	<0.001*
	F.I.	20	101.941	23.0112	
The mean values of serum IMA among patients with fatty liver disease by abdominal ultrasound were higher than their values among patients without fatty liver disease by abdominal ultrasounds with P value<0.001 which is statistically significant , so there is strong positive correlation between serum IMA and fatty liver as a complication of DM.					

Table 16: Ability of IMA to predict fatty liver.

	AUC*	**95% CI**	**P value**	**Cut-Off**	**Sensitivity**	**Specificity**
IMA	0.820	0.726– 0.914	**<0.001***	80.6	72.7%	74.5%
The ability of serum IMA to predict fatty liver with AUC 0.820, 95%C.I 0.726-0.914 with P value <0.001 with sensitivity 72.7% and specificity 74.5%.						

Table 17: Serum IMA among different states of renal functions.

Group statistics					
	Group	**N**	**Mean**	**Std. Deviation**	**P value**
IMA	Group A and C: diabetics and controls without nephropathy	62	66.252	18.1416	<0.001*
	Group B: diabetics with nephropathy	29	125.434	8.4077	
CREAT	Group A and C: diabetics and controls without nephropathy	62	0.801	.1505	<0.001*
	Group B: diabetics with nephropathy	29	4.295	1.6258	
Significant difference of serum IMA in group B than that of group A and group C with P value <0.001 which is statistically significant.					

Table 18: Correlation between serum IMA and serum creatinine in the whole sample.

Correlations					
		CREAT			
IMA	Pearson Correlation	.765**			
	Sig. (2-tailed)	.000*			
	N	91			
	A moderate positive correlation exists between IMA and creatinine in the whole sample R=0.765 P <0.001				
		N	Mean	Std. Deviation	P value
IMA	Group A: diabetics without nephropathy (63.8-105.2 U/ml)	33	81.018	10.9490	<0.001*
	Group B: diabetics with nephropathy (106-140 U/ml)	29	125.434	8.4077	
	Group C: Controls (40-60 U/ml)	29	49.448	5.5295	
	Total	91	85.112	31.8435	
CREAT	Group A: diabetics without nephropathy (63.8-105.2 U/ml)	33	.808	.1733	<0.001*
	Group B: diabetics with nephropathy (106-140 U/ml)	29	4.295	1.6258	
	Group C: Controls (40-60 U/ml)	29	.793	.1223	
	Total	91	1.914	1.8757	
A moderate positive correlation exits between serum IMA and creatinine in the whole sample with P value <0.001 and R=0.765 which is statistically significant , The serum IMA is higher in group B than that in group A and C which is statistically significant.					

Table 19: Ability of IMA to predict Nephropathy.

	AUC*	95% CI	P value	Cut-Off	Sensitivity	Specificity
IMA	1.000	1.000– 1.000	**<0.001***	105.6	100%	100%
Excellent ability of IMA to predict nephropathy (p value <0.001) (AUC > 0.7)						

and group A, also between group A and group C with P values<0.001 this was supported and agreed by Ahmed et al. [32-34], also significant difference was observed between serum creatinine in group B than that in group A and group C this was supported and agreed by Ahmed et al. [32], Moreover there is significant positive correlation between serum IMA and serum creatinine in the three groups which is significant statistically, this were supported and agreed by Ahmed et al. [32], the correlations of serum IMA and various parameters in the whole population of study showed a positive correlations between serum IMA and UAC ratio (p value<0.05, r=0.734) which is statistically significant, also it showed positive correlation between serum IMA, and serum creatinine (p<0.05, r=0.765) which is statistically significant these results were supported and agreed by Ahmed et al. [32], The ability of serum ischemia modified albumin to detect diabetic nephropathy with 95% confidence interval equals 1 with (p value<0.001) with (AUC>0.7) with 100% specificity and 100% sensitivity, this was supported and agreed by Ahmed et al. [32], The positive correlation between IMA and the UAC ratio implies that IMA increased progressively with the degree of albuminuria. This was supported by Krzystek-Korpacka et al. [16-32]. Results relating serum IMA to the presence of diabetic peripheral neuropathy by neurological examination and others who haven't diabetic peripheral neuropathy, showed that also the ability of serum IMA to predict diabetic peripheral neuropathy had sensitivity and specificity of 62.5% and 62.7%, furthermore, serum IMA among patients with diabetic retinopathy was significantly higher than those with normal retina (125.13 vs. 69.95)(P<0.001)· Also, the ability of serum IMA to predict diabetic retinopathy with AUC 0.962, 95% C.I 0.919-1.00, cut-off 111.7 had 96% sensitivity and 95.5% specificity, these results were supported by Turk et al. [35,36]. Also relating serum IMA to abnormal finding on abdominal ultrasound as fatty liver as a complication of diabetes mellitus showed positive correlation between serum IMA and fatty liver by p value<0.001 which is statistically significant, Moreover the ability of serum IMA to predict fatty liver with AUC 0.820, 95% C.I 0.726 - 0.914, had sensitivity of 72.7 % and specificity of 74.5%, these were agreed and supported by Amirtharaj et al. [37].

Conclusion

There is positive predictive value of serum IMA to detect diabetic microvascular complications as diabetic nephropathy, neuropathy and retinopathy.

Ethical Aspects

Research protocols were approved by the medical ethics committee of Kasr al Aini Medical School, Cairo University. All participants provided a written informed consent after the research protocols were explained carefully to them. Informed consent was obtained from all the study participants and their approval was taken by signature.

Conflicts

No conflicts of interest.

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