Original Research Article

Association between albumin creatinine ratio and e-GFR in type 2 diabetes mellitus patients in Oredo Local Government Area, Benin City, South-South Nigeria.

ABSTRACT

BACKGROUND: Diabetes mellitus is the commonest endocrine disease in Nigeria.

Nephropathy is one of the complications of type 2 diabetes mellitus that could lead to end stage renal disease. Persistent microalbuminuria is a predictor of high risk of developing diabetic nephropathy. Early detection of kidney disease and intervention will prevent progression to end stage renal disease.

OBJECTIVE: To determine the association between albumin creatinine ratio and eGFR in type 2 diabetic patients, their usefulness as early predictors of diabetic nephropathy and progression of disease.

MATERIALS AND METHODS: This was a cross sectional study conducted in the State Specialist Hospital, Benin City, Edo State, Nigeria. Forty six type 2 diabetes mellitus patients, both male and female within the age range of 30 – 85 years were recruited for the study, after meeting the inclusion criteria. Twenty age and gender matched healthy subjects were selected as controls. Fasting plasma glucose, glycatedhaemoglobin, C-Reactive protein, serum creatinine were assayed. Urine albumin was estimated and albumin creatinine ratio determined, eGFR was estimated according to the Modification of Diet in Renal Disease (MDRD) formula.

RESULTS:

There was a significant difference between means of glycatedhaemoglobin, C – Reactive protein, Albumin creatinine ratio, eGFR of subjectswhich was (8.3±2.1%,17.

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9±1.3mg/l,247.7±22.2mg/g,88±5.9ml/min) respectivelyand that ofcontrolswhich was (4.5±1.1%, 10.2±2mg/l,22.7±5.1mg/g, 93.1±2.3ml/min) p<0.05 .ACR showed a strong and linear negative correlation with eGFR (r=-.682, p<0.05).A higher percentage of patients (64.7%) with e-GFR<60 ml/min had microalbuminuria,compared with (57.7%) with microalbuminuria in the subjects with eGFR>60 ml/min. ~~Micro~~~~Aa~~Albuminuria worsened with increased duration of disease, as 55.6% of patients with diabetes mellitus of 5 years and above had macro albuminuria compared with 25% of patients with disease less than 5 years. Decline in eGFR increased with increasing duration of disease, 55.6% with disease duration of 5 years and above had eGFR<60ml/min, compared with 45.5% in those with disease less than 5 years.

Conclusion: Albumin creatinine ratio and eGFR had a significant and linear negative correlation in this study. Therefore, they could be useful as predictors of early kidney disease in type 2 diabetes mellitus in this local government area. Increase in severity of ~~micro~~albuminuria, coupled with higher prevalence of decline in eGFR with increasing duration of disease may be suggestive of their usefulness as predictors of disease progression.

Key words: Albumin creatinine ratio(ACR), eGFR, diabetes mellitus type 2.

Introduction

Diabetes mellitus is a chronic disease with an increasing prevalence worldwide. The prevalence in Nigeria varies from 0.65% in rural areas and villages to 11.0% in urban Lagos[1]. Good glycaemic control and control of other cardiovascular risks in diabetic patients lead to reduced morbidity and mortality[2].

Diabetic nephropathy is the leading cause of end stage renal disease worldwide[3]. It is said to affect 25-40% of diabetic patients[4]. The incidence of end stage renal failure due to diabetes has increased during the past two decades[5]. Roughly 50% of the end stage renal disease due to diabetes mellitus is associated with type 2 diabetes mellitus[6]. To prevent this increase, screening for chronic kidney disease and early intervention is necessary[5]. In diabetic patients, the early detection of diabetic nephropathy has been focused on measurement of urinary albumin excretion rate[5]

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. The detection of elevated urinary albumin excretion rate identifies patients with an increased risk for progression of diabetic nephropathy. The course of kidney function in type 2 diabetic patients with albuminuria is characterized by a highly variable but relentless decline in glomerular filteration rate and a concomitant rise in albuminuria and arterial pressure.[6,7,8] Previous studies have suggested that arterial blood pressure and albuminuria both act as progression promoters [7]. The National Kidney Foundation has recommended that diabetics should be screened annually for kidney disease [8].

The aim of this study was to determine the association between eGFR and albumin creatinine ratio in type 2 diabetic patientsin this environment, and its usefulness as markers for early detection of renal impairment in diabetics and its possible use as predictors of disease progression.

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Subjects, Materials and Methods

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This was a cross sectional study carried out in the State Specialist hospital Benin City, Edo State, Nigeria. Study was carried out between September 2012 and April 2013. Consent for the study was obtained from the ethical committee of the hospital and informed consent obtained from the patients and controls.

Forty-six type 2 diabetic patients both male and female aged 38 to 83 years were recruited for the study. Every 3rd consenting patient was selected from those attending the diabetic outpatient clinic was selected for the study. They were patients who were already diagnosed and being managed as type 2 diabetic patients. They have been diabetic for a mean duration of 5 years and 3 months. Structured questionnaires were used to obtain vital information from the patients, which included duration of disease, type of medications they are on, history suggestive of complications. General physical examination was performed on the patients and parameters such as height and weight were measured with a stadiometer and weighing scale respectively, blood pressure was measured with a sphygmomanometer.

Exclusion criteria

Subjects with proven urinary tract infection, diagnosed kidney disease other than diabetic nephropathy, concurrent acute illnesses including infectious diseases, ma

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lignancy, acute immunological disease, history of clinical cardiovascular disease, tuberculosis and smoking were excluded from the study.

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Twenty age and gender matched controls were involved in the study. They were not known diabetics, hypertensive nor had chronic kidney diseases.

SAMPLE COLLECTION

10ml of fasting venous blood was collected from the patients in the morning. 2.5 ml each was dispensed into lithium heparin,fluoride oxalate, ethylene diaminetetracetate (EDTA) and plain bottles. ~~The samples in fluoride oxalate,lithium heparin and EDTA bottles were inverted 8 to 10 times to ensure proper mixture of blood and anticoagulants~~. Samples in the EDTA bottle was immediately refrigerated at 4^0C, while that in the plain bottle were allowed to clot and then centrifuged at 3000 rpm for 5 minutes, separated into clean plain tubes and kept in an ultradfrizer at -80^0C till time of analysis.Samples in the lithium heparin and fluoride oxalate bottles were also centrifuged at 3000rpm for 5 minutes and plasma separated into clean plain tubes and stored in an ultradfrizer at -80^0C until time of analysis. First void morning urine was collected in a universal bottle with preservative.

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METHODOLOGY

Plasma glucose was assayed by the glucose oxidase method. Glycated hemoglobin was assayed by the boronate affinity method using the Kit (in-2-it system from Bio-rad). Marker of inflammation C-reactive protein was measured by latex enhanced turbidimmunometric assay.

Urinary Albumin excretion was measured using first void morning urine sample by the Lowry method[9], serum and urinary creatinine were assayed by modified Jaffe kinetic method.

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eGFR was calculated using the Modification of diet in Renal Disease (MDRD) equation [10,11].

GFR(ml/min/1.73m^2)=175 x Serum creatinine(mg/dl)$^{-1.154}$xAge in years$^{-0.203}$ x 0.742 (if female) x (1.212 if black).

STATISTICAL ANALYSIS

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This was done using SPSS version 13, means of variables are reported as mean ± standard deviation. Test of significance differences between means of variables was determined using the student 'T' test and ANOVA. A value of ≤0.05 was considered significant. Pearson's correlation was used in analyzing correlation between variables.

Results

A total of 46 diabetic subjects participated in the study, with 38.1% males and 61.9% females, all in the age range of 38 to 83 years. Mean age was 58.3 ± 1.2 years (Table 1). Twenty six of them were on angiotensin converting enzyme (ACE) inhibitors

Mean fasting plasma glucose, glycatedhaemoglobin and body mass index (BMI) of the subjects was 7.9± 0.4 mmol/l, 8.3 ± 2.1% and 27.6 ± 6.5 kg/m^2 respectively .(Table 1)

Mean albumin creatinine ratio and C-reactive protein of the subjects were 247.7 ± 22.2mg/g and 17.9 ± 1.3mg/l respectively.There was a statistically significant difference between the mean and controls ($p < 0.05$). (Table 1)

Figure 1 shows regression curve between albumin creatinine ratio and eGFR in the diabetic subjects~~patients~~.

eGFR showed a significant negative correlation with ACR in the subjects studied ($r = -0.681$, $p < 0.05$) while systolic blood pressure showed a significant positive correlation with ACR, $r = .506$, $p < 0.05$. ~~(Table 2)~~

While 57.7% of the patients with eGFR≥ 60 ml/min had microalbuminuria, 42.3 had macroalbuminuria. 64.7% of patients with eGFR<60ml/min had microalbuminuria and 35.3% had macroalbuminuria. (Table ~~3~~2)

75% of the patients with diabetes for less than 5 years had microalbuminuria and macroalbuminuria, while 25% had macroalbuminuria. 44.4% of those with diabetes mellitus of 5 years and above had microalbuminuria and 55.6% macroalbuminuria. 54.5% of patients with diabetes mellitus of below 5 years duration had e GFR

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of ≥ 60ml/min while 45.5% had eGFR< 60ml / min. Also 44.4% of those with diabetes of 5 years and above had e GFR ≥ 60ml / min, and 55.6% had e GFR < 60ml / min.(figures 2a and 2b)(table 43).

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DISCUSSION

Diabetic nephropathy is a common complication of type 2 diabetes mellitus. Good glycaemic control and screening for early detection of diabetic nephropathy will reduce morbidity, progression to end stage renal disease and mortality.The National kidney Foundation (NKF) and American Diabetic Association (ADA) recommends that annual screening of patients diagnosed as diabetic for albumin creatinine ratio and eGFR is ideal. Also the American Diabetic Association recommends annual screening to assess urine albumin excretion in all type 2 diabetic patients,starting at diagnosis.[12]

There was a significant difference between the body mass index(BMI), glycatedhaemoglobin, ACR, eGFR and C-reactive protein of the subjects and controls in this study. Our findings corroborate what other studies have revealed[14,16].The significant difference observed between mean BMI and mean CRP of subjects and controls, may be indicative of the roles they play in pathogenesis of diabetes mellitus.Hu FB [17] in their study on " inflammatory markers and risk of developing type 2 diabetes in women in the USA" reported that elevated plasma levels of CRP were an independent predictor of type 2 diabetes mellitus in apparently healthy women. Wang Z [18] also reported in the study on aboriginal Australians, that CRP is independently associated with development of diabetes in the aboriginal people.

We observed a significant difference between albumin creatinine ratio and eGFR of subjects and controls, this may be suggestive of varying degrees of renal impairment in these patients. None of the patients in this study was normoalbuminuric, they already had varying degrees of microalbuminuria as at the time of the study. This may be a reflection of the degree of prevalence of renal impairment among t

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hese subjects~~patients~~, and it highlights the need for screening for microalbuminuria in all newly diagnosed diabetics, and annual screening in all diabetics, for early detection of kidney disease or prevention of progression to end stage renal disease as recommended by the National Kidney Foundation[8] and American Diabetic Association [12].Whether APOL 1 and MHY 9 genes could be contributory factors to the prevalence of renal impairment in these subjects was not ascertained in this study. However, studies have shown the roles these genes could play in the development of diabetic nephropathy in Africans. Palmer ND[19] et al in their study reported that variants in MHY 9 genes played the most significant role in the development of nephropathy.

Estimated glomerular filteration rate (eGFR) showed a significant negative correlation with albumin creatinine ratio, with decline in eGFR , ACR increased. Other studies have reported similar findings~~19~~[20]. Decline in eGFR therefore may also be useful as a marker for early detection of renal impairment in type 2 diabetes patients, in conjunction with albuminuria just as the study by Berhane A and coauthors~~20~~[21] reported in Pima Indians with type 2 diabetes. They reported in their study that a combined measure of albuminuria and eGFR is a significantly better predictor of end stage renal disease.

~~Following~~With the National Kidney Foundation recommendation that diabetics should be screened annually for kidney disease, which includes ACR, serum creatinine and eGFR measurements, ~~and the screening should include measurement of ACR in a spot urine sample, measurement of serum creatinine and e-GFR,~~ the observation from this study shows that estimation of albumin creatinine ratio and e-GFR could be useful markers in this environment for early detection of diabetic nephropathy, prevention of overt nephropathy and progression to end stage renal disease. This is very important as these tests are relatively cheaper and therefore more affordable compared with other diagnostic tests such as magnetic resonance imaging, computerized to~~u~~mography scan, which are more expensive and may not be readily affordable by people of lower socioeconomic group. Also they serve as cheaper screening tests for early detection of renal impairment, and therefore prevent increased incidence of chronic kidney disease or end stage renal disease. Chronic kidney disease which is still largely managed in this environment by dialysis is n

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ot easily affordable for patients of low socioeconomic group, therefore simple screening tests like this will go a long way in early detection and intervention to prevent chronic kidney disease. Moreover, it was observed that while 57.7% of the patients with eGFR≥ 60ml / min had microalbuminuria, a larger percentage (64.7%) had microalbuminuria in those with eGFR< 60ml/min, prevalence of albuminuria increased with duration of disease. This still shows the roles the two factors could play in the detection of kidney disease and its progression. Per K[6]and coauthors reported a more rapid decline in GFR and progressive rise in albuminuria in type 2 diabetes mellitus with glomerulopathy, compared with those without glomerulopathy , indicating the roles microalbuminuria and eGFR could play as progression promoters.

When a comparison was done between patients with diabetes of below 5 years, and those of 5 years and above, the role these two factors play was better highlighted. A higher percentage of patients with diabetes of 5 years and above had macroalbuminuria, compared with those below 5 years, indicating that with increasing duration of disease the degree of albuminuria worsened.J.K Lutale[21]22 and coauthors in Tanzania reported the same finding that abnormal albumin excretion rate was significantly related to duration of diabetes. Similarly, a larger percentage of the subjects with diabetes of 5 years and above had eGFR< 60ml / min compared with those with diabetes of less than 5 years duration, showing a decline in e GFR with increasing duration of disease.

CONCLUSION

Albumin creatinine ratio showed a significant negative and linear correlation with eGFR in this study. They may be useful tools for screening and early detection of kidney disease in type 2 diabetes mellitus patient in this environment. Increased prevalence and severity of microalbuminuria and increased prevalence of decline in eGFR with increasing duration of disease, is suggestive that ACR measurements and eGFR estimation may be useful as predictors of disease progression in type 2 diabetes mellitus.The degree of prevalence of incipent nephropathy,and overt nephropathy in some cases,observed in some of the subjects in this study,calls~~a~~ for a review of guidelines for management of type 2 diabetic patients in this environment. Establishment of protocols for the management of these~~is~~ patients is advocate

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This should include screening of~~It is recommended that~~ type 2 diabetes mellitus patients ~~should be screened~~ annually for microalbuminuria and eGFR determined, for early detection and prevention~~alence~~ of kidney disease.

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Table 1:Demographic and Clinical Characteristics of the subjects

PARAMETER CONTROL	CONTROLS	SUBJECTS	p-VALUE
Male Population (%)	40	38.1	
Female Population (%)	60	61.9	
Age (Years)	56.1±1.0	58.3 ± 1.2	0.32
BMI (Kg/M^2)	23.2±1	27.6 ± 6.5	0.063
Systolic blood pressure(mmHg)	120.5±3	144±44	0.095
Diastolic blood pressure(mmHg)	76.8±2.5	84±10	0.630
Fasting Plasma Glucose(mmol/l)	4.6±1.1	7.9±0.4	0.001
GlycatedHaemoglobin(%)	4.5±1.1	8.3 ± 2.1	0.000
C – Reactive Protein (mg/l)	10.3 ± 2.0	17.9±1.3	0.005
Albumin Creatinine Ratio(mg/g)	22.7 ± 5.1	247.7±22.2	0.000
eGFR(ml/min)	93.1±2.3	88 ± 5.9	0.040

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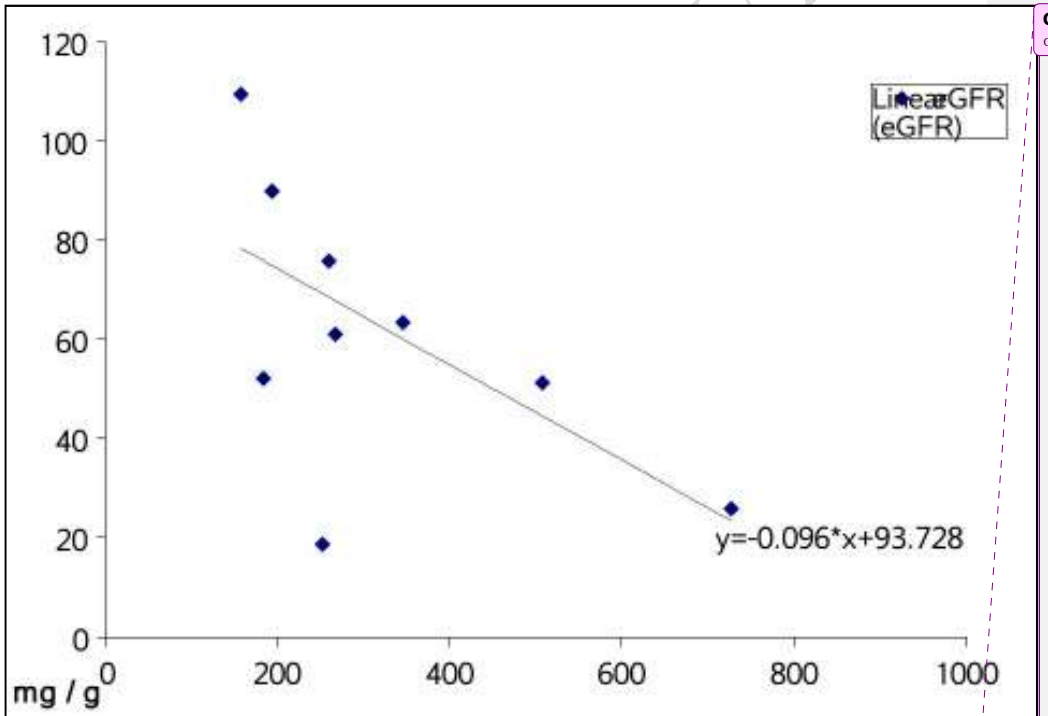

Fig 1 : Regression betwen ACR and eGFR

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~~Table 2 Correlation of eGFRand systolic blood pressure with Albumin CreatinineRa~~
~~tio.~~

~~Parameter~~	~~r~~	~~P-value~~
~~eGFR~~	~~.681~~	~~.021~~
~~Systolic Blood Pressure~~	~~.506~~	~~.006~~

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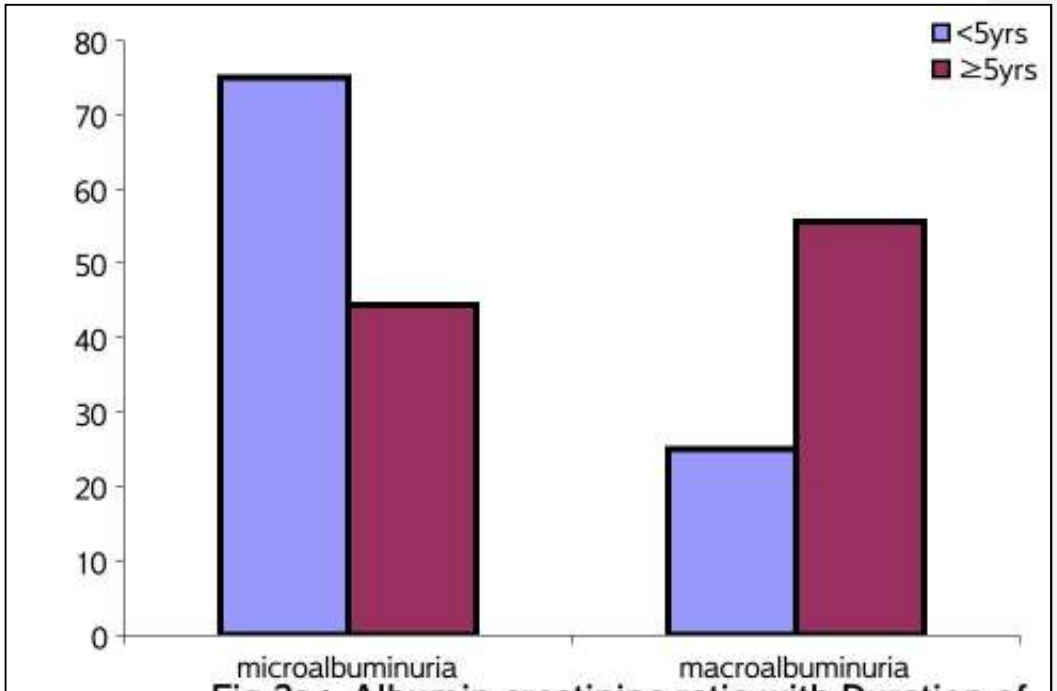

Fig 2a.: Albumin creatinine ratio with Duration of Disease in Subject

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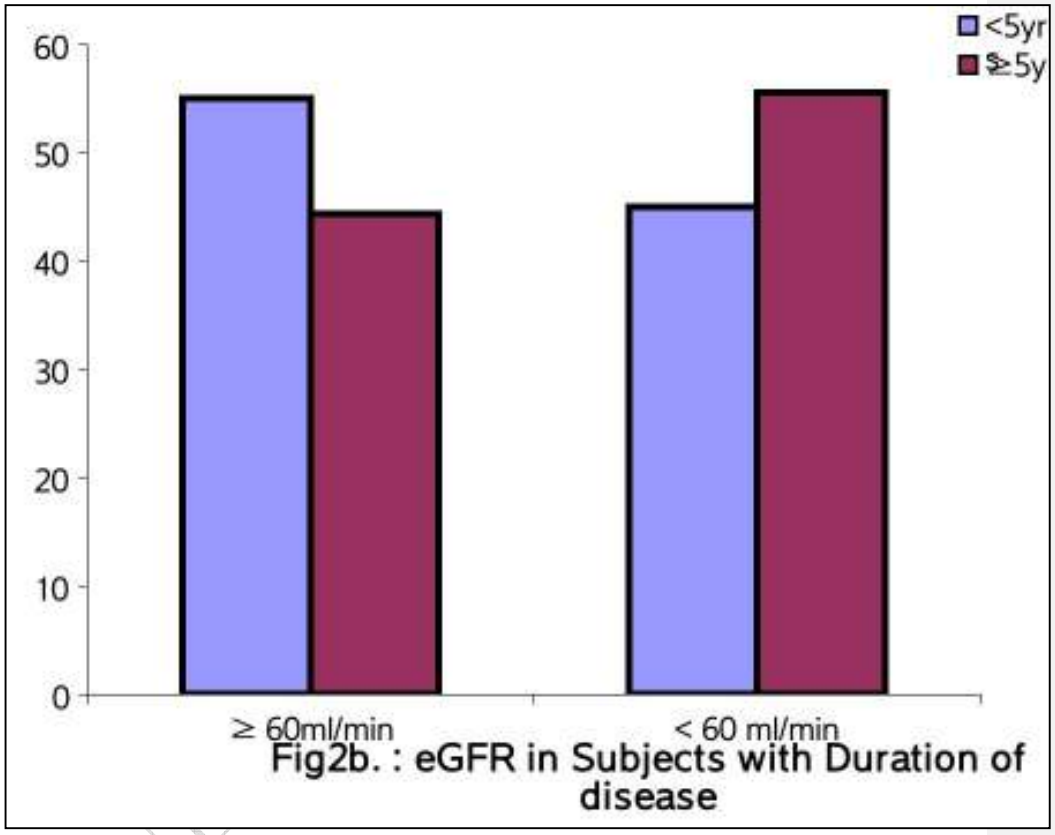

Fig2b. : eGFR in Subjects with Duration of disease

Table ~~3~~2

Association between eGFR and Urine albumin excretion rate in type 2 diabetic pat
ients

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	e GFR ≥ 60ml / min n = 26	e GFR < 60ml/min n = 17
Normoalbuminuria (<30mg/g)	0 (0%)	0 (0%)
Microalbuminuria (30 –299300mg / g)	15(57.7 %)	11 (64.7%)
Macroalbuminuria(≥≥ 300mg/g)	11(42.3%)	6(35.3%)

Table 43

ACR and eGFR in the Subjects based on duration of diabetes below 5 years and 5 yearsandabove

	Below 5 years N=22	5 years and above N=21
Microalbuminuria	17(75%)	10(44.4%)
Macroalbuminuria	5(25%)	11(55.6%)
eGFR≥60	12(54.5%)	10(44.4%)
eGFR<60	10(45.5%)	11(55.6%)

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