

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, glycated haemoglobin, 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 glycated haemoglobin, C – Reactive protein, Albumin creatinine ratio, eGFR of subjects ($8.3 \pm 2.1\%$, $17.9 \pm 1.3\text{mg}$

/l,247.7±22.2mg/g,88±5.9ml/min) and controls (4.5±1.1%, 10.2±2mg/l,22.7±5.1 mg/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. Microalbuminuria 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 microalbuminuria 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 Lagos¹. Good glycaemic control and control of other cardiovascular risks in diabetic patients lead to reduced morbidity and mortality².

Diabetic nephropathy is the leading cause of end stage renal disease worldwide³. It is said to affect 25-40% of diabetic patients⁴. The incidence of end stage renal failure due to diabetes has increased during the past two decades⁵. Roughly 50% of the end stage renal disease due to diabetes mellitus is associated with type 2 diabetes mellitus⁶. To prevent this increase, screening for chronic kidney disease and early intervention is necessary⁵. In diabetic patients, the early detection of diabetic nephropathy has been focused on measurement of urinary albumin excretion rate

te⁵. 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 filtration 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 promoters⁷. The National Kidney Foundation has recommended that diabetics should be screened annually for kidney disease⁸.

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

Subjects, Materials and Methods

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

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

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 diaminetetraacetate (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 were immediately refrigerated at 4°C, 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°C 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°C until time of analysis. First void morning urine was collected in a universal bottle with preservative.

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 method⁹, serum and urinary creatinine were assayed by modified Jaffe kinetic method.

eGFR was calculated using the Modification of diet in Renal Disease (MDRD) equation^{10,11}.

$$\text{GFR}(\text{ml}/\text{min}/1.73\text{m}^2) = 175 \times \text{Serum creatinine}(\text{mg}/\text{dl})^{-1.154} \times \text{Age in years}^{-0.203} \times 0.742$$

(if female) $\times (1.212$ if black).

STATISTICAL ANALYSIS

This was done using SPSS version 13, means of variables are reported as mean $\pm$ 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 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).

Mean fasting plasma glucose, glycated haemoglobin and body mass index (BMI) of the subjects was 7.9 ± 0.4 mmol/l, $8.3 \pm 2.1\%$ and 27.6 ± 6.5 kg/m² respectively. (Table 1)

Mean albumin creatinine ratio and C-reactive protein of the subjects were 247.7 ± 22.2 mg/g and 17.9 ± 1.3 mg/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 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 $eGFR \geq 60$ ml/min had microalbuminuria, 42.3% had macroalbuminuria. 64.7% of patients with $eGFR < 60$ ml/min had microalbuminuria and 35.3% had macroalbuminuria. (Table 3)

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 eGFR of ≥ 60 ml/min while 45.5% had $eGFR < 60$ ml/min. Also 44.4% of those with diabetes of 5 years and above had $eGFR \geq 60$ ml/min, and 55.6% had $eGFR < 60$ ml/min.

min.(figures 2a and 2b)(table 4).

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), glycated haemoglobin, 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. Hui et al¹⁷ 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 et al¹⁸ 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 these patients, and it highlights the need for screening for microalbuminuria in all newly diagnosed diabetics, and annual screening in all diabetics, for early detection

n of kidney disease or prevention of progression to end stage renal disease as recommended by the National Kidney Foundation⁸ and American Diabetic Association¹².

Estimated glomerular filtration rate (eGFR) showed a significant negative correlation with albumin creatinine ratio, with decline in eGFR, ACR increased. Other studies have reported similar findings¹⁹. 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 coauthors²⁰ 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 the National Kidney Foundation recommendation that diabetics should be screened annually for kidney disease, 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 tomography 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 not 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 $\text{eGFR} \geq 60 \text{ ml/min}$ had microalbuminuria, a larger percentage (64.7%) had microalbuminuria in those with $\text{eGFR} < 60 \text{ ml/min}$, 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 K⁶ and coauthors reported a more rapid decline in GFR and progressive rise in album

inuria in type 2 diabetes mellitus with glomerulopathy, compared with those with out glomerulopathy , indicating the roles microalbuminuria and eGFR could play a s 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 Lutale²¹ 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. It is recommended that type 2 diabetes mellitus patients should be screened annually for microalbuminuria and eGFR determined, for early detection and prevalence of kidney disease.

REFERENCES

1. Akinkugbe O.O. Final report on national survey on communicable diseases in Nigeria, Series 1. Federal Ministry of health and social services, Lagos; 1997.
2. Chineye S, Uloko A E, Ogbera A O, Ofoegbu E N, Fasanmade A A, et al:

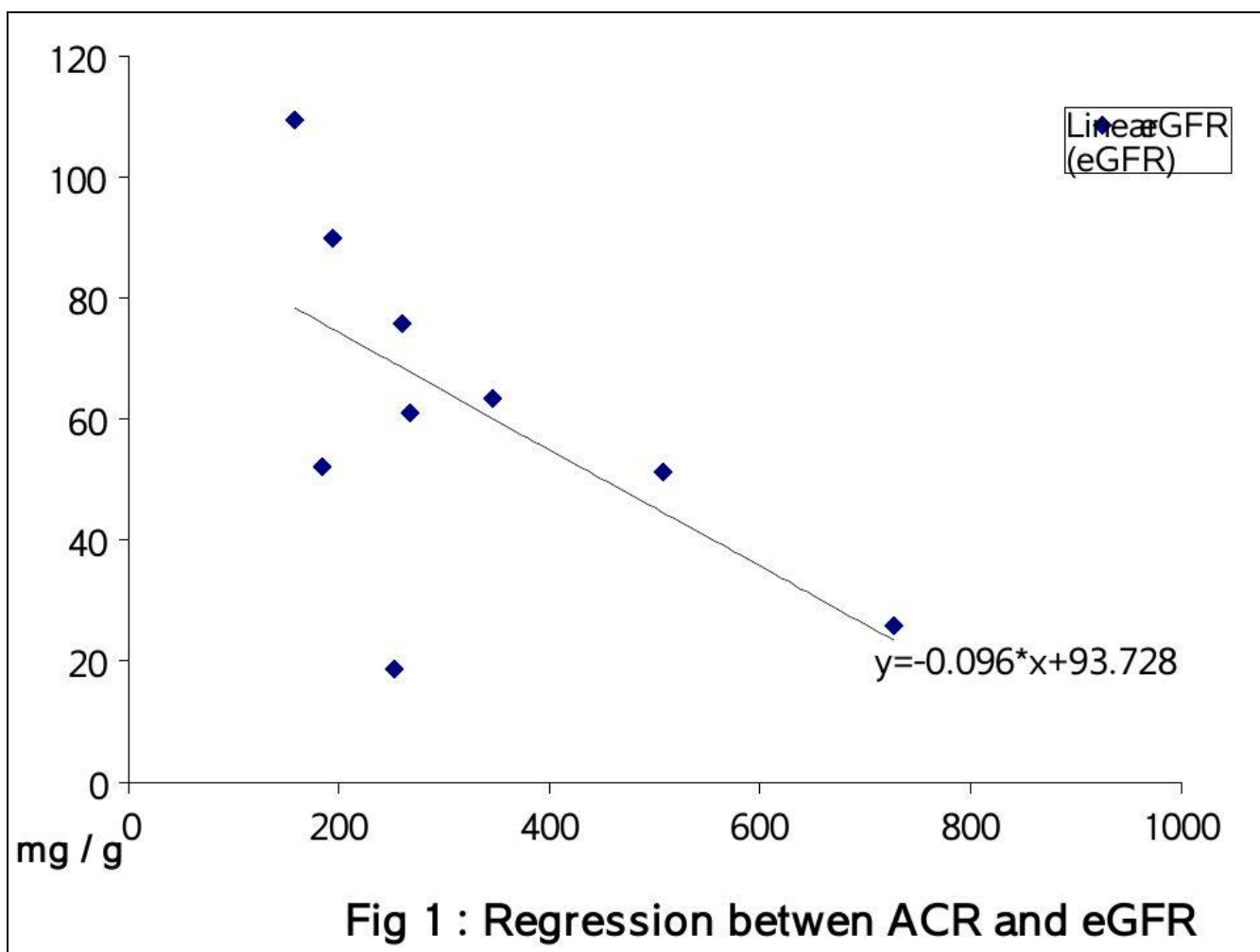
Profile of Nigerians with diabetes mellitus . Diabetes Nigeria Study group (2008): Results of multi centre study. Indian J Endocrinol metab. 2012; 16 (6): 981

3. Khan M.I, Usman K, Ashfaq F, Himansho D, Ali W, Idris M Z. Association of Hs-CRP and HbA1c with microalbuminuria in type 2 diabetic patients in North India. Bio Med Research 2012; 23 (3): 380-384.
4. Rigalleau. V, Lasseur C, Perlemoine C, Barthe N, Raffin C, Elin C. Estimation of glomerular filtration rate in diabetic subjects. Cockcroft formula or modification of diet in renal study equation. Diabetes care April 2005 vol 28 no 4 838-843
5. Konrad Walczak, Malgerzater Soldolska, Izabela Majerek, Anna Krysicka, Dariusz Moczul. Diabet Doswi Klin 2008 Vol 8, No 4 165 – 168. ISSN 1643 – 3165.
6. Per K. Christensen, Gall M, Parving H.H. course of glomerular filtration rage in albuminuric type 2 diabetic patients with or without glomenlopathy. Diet care. 2000 vol 23 page 2: B14 – B20.
7. Yokoyama H, Tomonaga O, Hirayama M, Ishii A, Takeda M, Babazono T, et al. Predictors of the progression of diabetes nephropathy and the beneficial effect of angiotensin – converting enzyme inhibitors in NIDDM patients Diabetologia. 1997 April; 40 (4): 405 – 411, 1997
8. National kidney foundation. KDOQ1 clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007; 4a (Suppl 2) S21 – S139.
9. Lowry OH, Rosebrough NJ, Randall RJ. Protein Measurement with the folin phenol reagent. J. Biol.Chem 1951: 193: 265 – 275.
- 10.National kidney disease education program. Estimating GFR. nckidney.nin.gov/lab.2014.
- 11.Levey AS, Coresh T, Greene T, Stevens LA, Zhans YL, Hendriksen S et al. Chronic kidney disease epidemiology collaboration. Using standardized serum creatinine values in modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann intern med 2006. 145 (4): 247 -254.
- 12.American Diabetes Association. Standards of medical care in

- diabetes. *Diabetes Care*. 2008. 31 (Suppl 1) S1 – S11.
13. Amanullah S, Jarari A, Govindan M, Basha M.I, Khateeja S. Association of hs-CRP with diabetic and non-diabetic individuals. *Jordan J. Bio Sci* 2010. Vol 3 Pg 7-12.
14. Aggarwal T, Kumar M. Prevalence of Microalbuminuria among Rural North Indian population with Diabetes mellitus and its correlation with glycosylated haemoglobin and smoking. *J. Clin. Diagn. Res* July 2014, 8 (7).
15. Zabeen S, Rahman M R, Narsis W, Mustafa T G, Eucufzei N H. GFR and cardiovascular events in type 2 diabetes mellitus. *AKMMC J* 2011; 2 (1): 06-08
16. Hambeli Z. High sensitivity C-reactive protein in diabetes mellitus type 2 according to micral test findings. *Ends Abs* 2007 (14) P96.
17. Hu F B, Meigs J B, Li Ty, Rifai N, Mason J E. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004 mar, 53 (3): 693 – 700.
18. Wang Z, Hoy W E. C-reactive protein and the risk of developing type 2 diabetes in aboriginal Australians. 2006. *Diab Res Clin Prac*. doi.10. 1016/J. diabetes 2006. 07108.
19. Meguro S, Tomita M, Kabeya Y, Katsuki T, Oikawa Y, Shimade A, et al. Factors associated with the decline of kidney function differs among e GFR strata in subjects with type 2 diabetes mellitus. *Int . J . Endo* vol 2012 (2012). Article ID 687867, 6 Pages.
20. Berhane A, Well J, Knowler W, Nelson R, Hanson R. eGFR predict kidney failure in pima Indians with type 2 diabetes mellitus. *Clin J. Am So . Nephrol* oct 2011; 6 (10): 2444 – 2451.
21. Abbas G, Lutale J K, Thordeson H, Vetvik K. Microalbuminuria among type 1 and type 2 diabetes patients of African origin in Dares Salam, Tanzania. 2007. *BMC nephrology* 2007. 8, 20.

Table 1: Demographic and Clinical Characteristics of the subjects

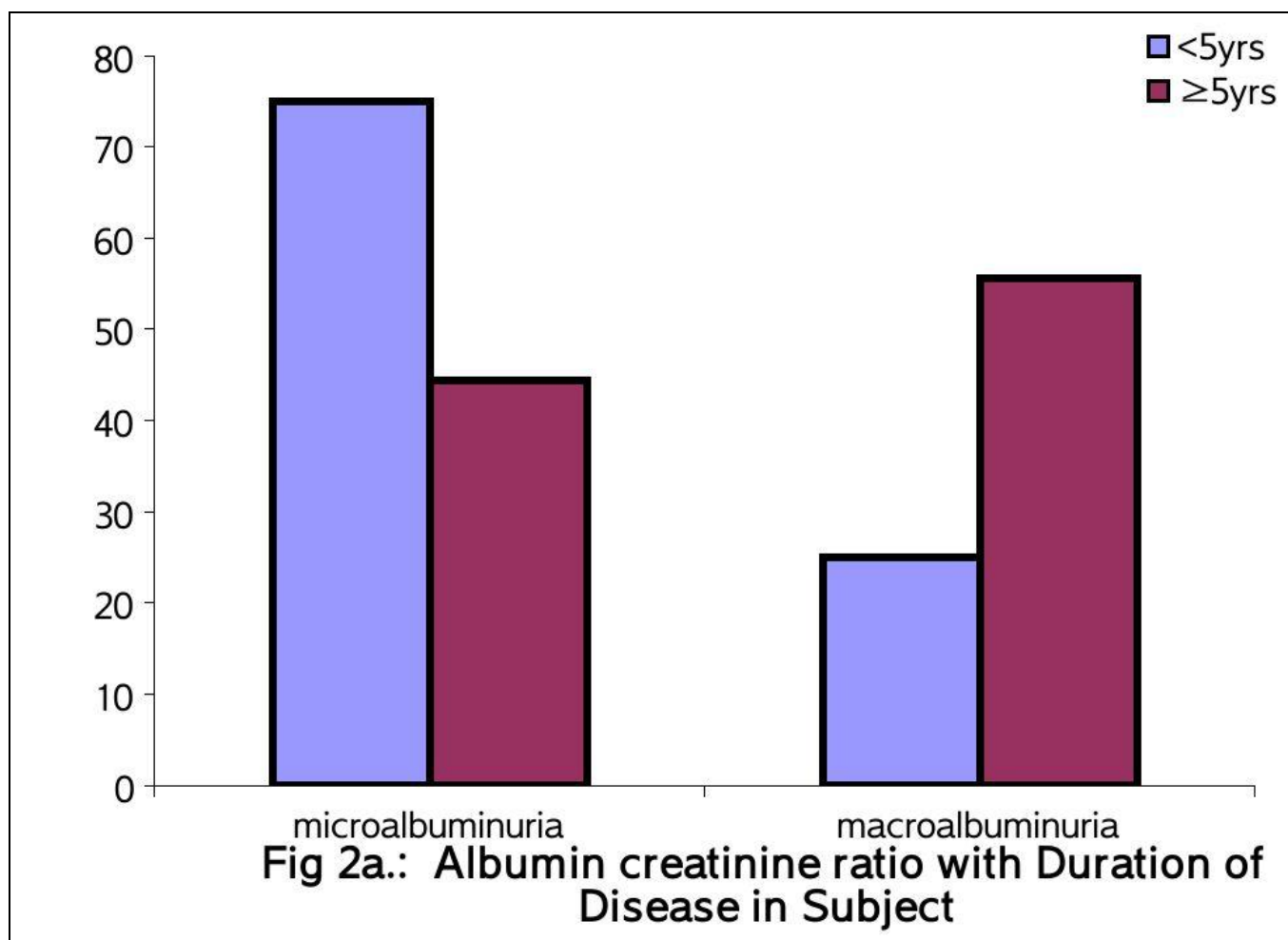
PARAMETER CONTROL	CONTROLS	SUBJECTS	p-VALUE
Male Population (%)	40	38.1	
Female Population (%)	60	61.9	
Age (Years)	56.1±1.0	58.3 ± 1.2	0.32
BMI (Kg/M ²)	23.2±1	27.6 ± 6.5	0.063
Systolic blood pressure(mmHg)	120.5±3	144±44	0.095
Diastolic blood pressure(mmHg)	76.8±2.5	84±10	0.630
Fasting Plasma Glucose(mmol/l)	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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Table 2 Correlation of eGFR and systolic blood pressure with Albumin Creatinine Ratio.

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



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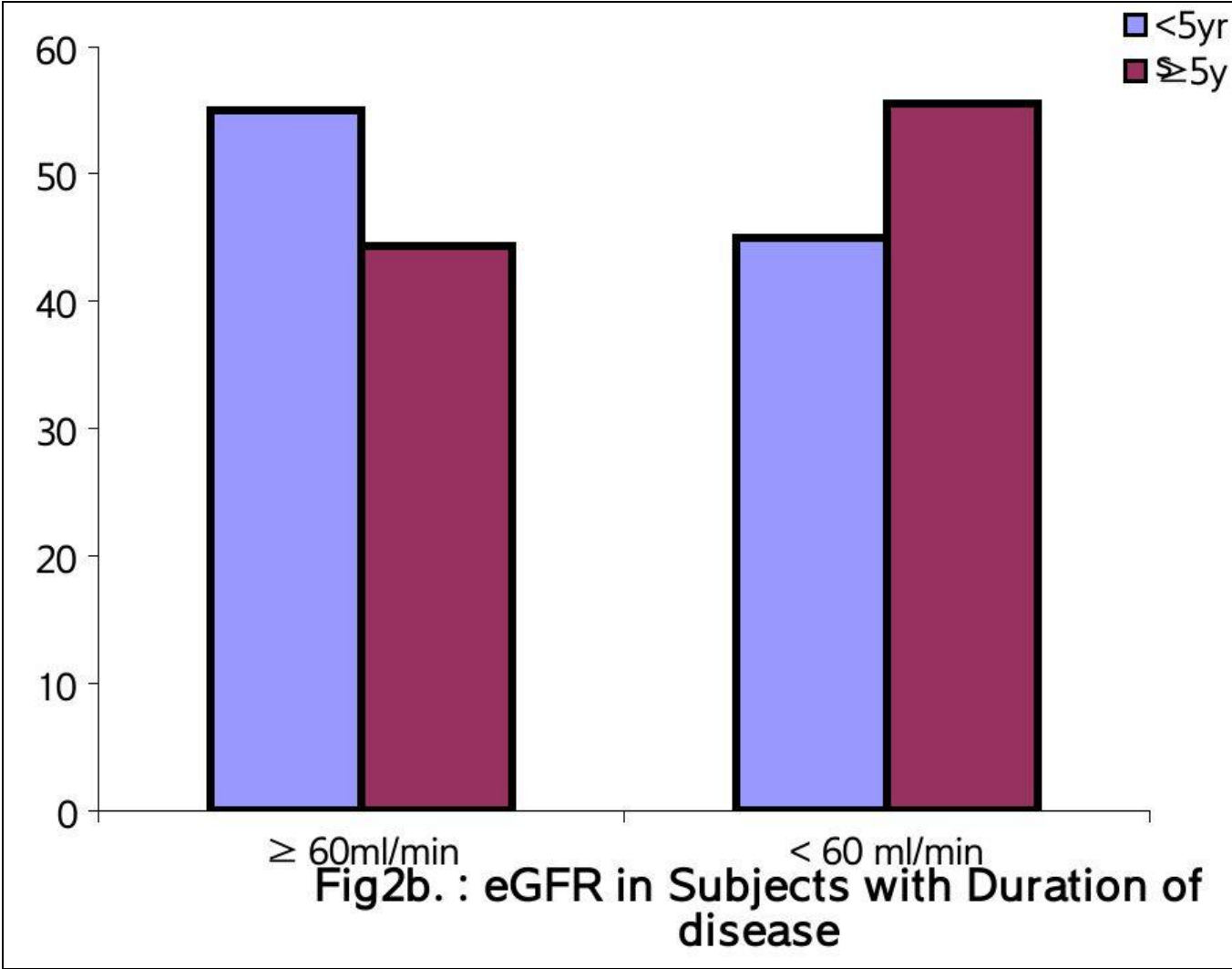
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359 Table 3

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

	e GFR $\geq$ 60ml / min n = 26	e GFR < 60ml/min n = 17
Normoalbuminuria (<30mg/g)	0 (0%)	0 (0%)
Microalbuminuria (30 – 299mg / g)	15(57.7%)	11 (64.7%)
Macroalbuminuria($\geq$ 300mg/g)	11(42.3%)	6(35.3%)

Table 4

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

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