International J. of Healthcare & Biomedical Research, Volume: 1, Issue: 3, April 2013, Pages 109-119

"Microalbuminuria and its association with risk factors among type 1 diabetes mellitus patients attending a tertiary care hospital : A cross sectional study"

[1]Reshu Gupta*, [2]Abhishek kawatra,[3] S. Gehlot, [4]R.P.Agrawal, [5]B.K.Binawara, [6]Himanshu Sharma

[1] PhD (MEDICAL) PHYSIOLOGY,
[2] MD PSM ,ASSISTANT PROFESSOR
[3] MD ,PHYSIOLOGY. PROFESSOR
[4] M.D., MEDICINE PROFESSOR
[5]M.D., PHYSIOLOGY ASSOCIATE PROFESSOR
[6] POST GRADUATE STUDENT , PHYSIOLOGY
*Dept. of physiology M.G. Medical College and Hospital.
Mahatama Gandhi University of Medical sciences and Technology. Jaipur
***Correspondence** : Dr Reshu Gupta ; **Email**: reshugpt@gmail.com

ABSTRACT

Background: Owing to few reports on the prevalence of microalbuminuria in Type 1 diabetic subjects in North-West India, we intended to study various degrees of microalbuminuria in type 1 diabetic subjects and to study the same with various risk factors.

Methods: All the type 1 diabetic patients attending Diabetic Care Research Center during three months were enrolled in the present study. The patients who did not meet the inclusion criterias were excluded. Eligible population sample accounted at 100 patients. The various parameters studied were Anthropometeric indices, Blood pressure, retinopathy, glycaemic status and lipid profile. Microalbuminuria estimation was done by Micral test. Appropriate statistical test like mean, Standard error, students t test and regression analysis was applied.

Results: Microalbuminuria was seen in 38% patients. The mean urinary albumin concentration in Microalbuminuric cases, hypertensive patients and normal individuals was reported as 96.61 mg/L, 134 mg/L and 74.5 mg/L respectively. Mean diabetic duration was 6.43 years in Microalbuminuric. Albumin excretion increased significantly with age at onset of 10-18 years and declined thereafter. Microalbuminuria cases exhibited mean cholesterol level as 181.63 mg%, TG 130.94 mg%, LDL 109.87 mg%, HDL 57.5 mg% and VLDL 30.64 mg%. Mean urinary albumin concentration in patients with retinopathy and without retinopathy was 160.52 mg/L and 78.66 mg/L respectively. In multiple regression analysis, a strong association seen between Microalbuminuria and hypertension (OR=5.087, CI=2.1319-12.101), fasting blood sugar (OR=3. 491, CI=1.138-10.70), duration of diabetes (OR=3.41, CI=1.360-8.55) and HbA_1c (OR=2.381, CI-=1.1-5.64) was observed.

Conclusion: The present study indicates that microalbuminuria is common complication of type 1 diabetes mellitus and can be prevented by careful management of risk factors.

Keywords: Type 1 diabetes, microalbuminuria, diabetic nephropathy, retinopathy, hypertension

INTRODUCTION: It results from a progressive autoimmune process associated with destruction of the insulin producing beta cells of pancreas [1]. In the early stages of diabetic renal disease, increased urinary albumin excretion (defined as microalbuminuria) is likely to result from increased capillary pressure mediated transglomerular flux of albumin. As the degree of albuminuria worsens, there is progressive alterations of the glomerular filtration barrier, a loss of negative charge and enlargement of pore size

(possibly secondary to podocyte loss)[2]. Epidemiologic studies have demonstrated that 20-30% of all patients with type 1 diabetes mellitus (DM) with diseases duration of 20-30 years develop clinically significant renal diseases. The presence of Microalbuminuria is said to precede and predict overt diabetic nephropathy and is the most commonly used clinical marker, and can be seen in stage III of diabetic nephropathy. Several studies suggest that at these early stages progression of diabetic nephropathy can be prevented [3-5]. Estimates of the prevalence of Microalbuminuria in children vary between 7-28.2% in different studies, 2.4% patients aged less than 13 years [6],7% in subjects with duration of IDDM 3-9 years and 4% in 3-5 years [7],12.5% [8],16% [9],28.2% [10]. Diabetes mellitus is the commonest single cause of end stage renal failure, which is also associated with high morbidity and mortality. Diabetes mellitus is usually first recognized as proteinuria. Proteinuria refers to albustix positivity or albumin excretion rate >200 µg/min or > 300mg/24 hrs. Diabetics with albustix negative urine may have a preceding phase of increased urinary albumin excretion termed as Microalbuminuria. It is defined as albumin excretion rate > 20µg/min (or 30 mg/24 hrs) and <200µg/min (or <300 mg/24 hrs) with a negative Albustix. This risk of development of Microalbuminuria in type 1 diabetic patients has been reported in several studies from western countries and in a study from India [10]. Approximately 40% of all type 1 diabetic patients ultimately develop the clinical syndrome of diabetic nephropathy, associated with a progressive increase in urinary albumin excretion, accompanied with a rise in blood pressure and a relentless decline in glomerular filtration, culminating eventually in end stage renal failure [11]. It also encompasses a state of greatly increased cardiovascular risk, accompanied, if untreated, by a progressive decline in renal function and associated with diabetic retinopathy [12]. This cross sectional study was undertaken to establish the prevalence of Microalbuminuria in insulin dependent patients and correlate the prevalence and albumin excretion rate to demographic and clinical profile, glycaemic control and diabetic complications.

METHODOLOGY: The present study was a cross sectional hospital based study Conducted at Diabetes Care and research center, Bikaner, for a period of three months. The study was approved by the Ethical Committee of the S.P. Medical College; Bikaner. All the patients of type 1 diabetes, meeting the inclusion criteria, attending the Out Patient Department of the said center were enrolled in the study. The patients with urinary tract infection, renal, cardiac, hepatic diseases, any acute infection, any inflammatory process, malignant condition, those on nitrates/antioxidants and smokers were excluded from the study. Samples from pubertal girls during menses and any sample with hematuria were also not included for investigations. The total eligible population sample accounted at 100 in the age range of 2 to 43 years. Written informed consent was taken from all patients after explaining the whole procedure and motive of the study. The various clinical and laboratory based examinations were done on this sample of hundered type 1 diabetics patients. On the basis of Microalbuminuria estimation, these patients were

divided into two groups. Group A included the patients with Microalbuminuria and Group B without Microalbuminuria. These groups were divided for the study of associated risk factors. A detailed history of each patient was obtained regarding the age, sex, year of diagnosis of diabetes, age at onset, duration of diabetes, family history of diabetes, history of smoking and of any associated illness. BMI and W/H ratio were taken to measure the anthropometric parameter. Status of glycaemic control was estimated by measuring glycosylated hemoglobin (HbA_1C) by "Ion Exchange Chromatography" with HbA_1C kit and fasting blood sugar by "Glucose Oxidase Method" with semi auto analyzer.

Lipid profile viz. Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) and Triglyceride (TG) were estimated in serum calorimetrically using enzymatic kits. Systolic and Diastolic blood pressure was estimated by using Sphygmomanometer. Retinopathy was evaluated after full dilation of both the pupils by instillation of topical mydiatric (0.5% tropicamide with phenylephrine).

Early nephropathy was established by the presence of Microalbuminuria (Micral test) in early morning midstream urine samples. Because of variability in urinary albumin excretion, two of the three samples collected within a three to six months period were estimated.

STATISTICAL ANALYSIS: The data was encoded in the Microsoft excel sheet and subsequent analysis was done. Mean and standard Error was calculated. The tabulated quantitative data was analysed with application of unpaired student't'-test. Multiple logistic regression analysis was carried out to identify the parameters associated with Microalbuminuria and odds ratio was calculated.

OBSERVATION AND RESULTS: Out of 100 patients of type 1 diabetes mellitus, persistent Microalbuminuria was present in 38% (Group A =38) and Normoalbuminuria in 62% (Group B=62) patients. The demographic profile of the study population is shown in Table I. The mean age of the subjects in the Group A was 27.84±1.83 years while in Group B was 25.51±1.27 years. There was no significant difference in age amongst the two groups (Table-I). In the present study, 8 (21.05%) patients with a positive family history of diabetes mellitus had Microalbuminuria while only 12(19.35%) patients with a positive family history of diabetes mellitus had normoalbuminuria.

In the Group A the mean BMI was 21.05±0.76 Kg/m^2 which was slightly less than 21.46± 0.64 Kg/m^2 from the Group B, the difference between the two was statistically non significant (Table-I). In the present study, the mean age at onset in the Group A was 21.40± 1.76 years while in the Group B it was 22.72±1.27 years, the difference between the two groups being statistically non significant (p=0.65). The duration of diabetes was observed in Group A was 6.43±0.89 while in Group B it was 2.79±0.33 which was highly significant ($p<0.001$),it showed that the prevalence of Microalbuminuria was increased with increasing duration of diabetes(Table-I).The mean fasting blood sugar level in Group A was 203.45±12.17 while in Group B was 165.28±7.26,there was significant difference between these two

groups p<0.01 (Table-II).In this study there was a parallel increase in the prevalence of microalbuminuria and level of HbA_1C. The relationship was found to be highly significant p<0.001 (Table-II). In the present study, significant association was found between Total cholesterol (p<0.02), LDL cholesterol (p<0.02), triglycerides (p<0.005), VLDL cholesterol (p<0.02) HDL cholesterol (p<0.001) and Microalbuminuria (Table -II). The mean urinary albumin for patients without retinopathy was 78.66±16.32 mg/L but was almost twice i.e. 160.52±24.68 mg/L for patients with retinopathy. The difference between the two means was statistically significant (p<0.001). Thus it was concluded that as the degree of Microalbuminuria increases, the involvement of retina increases in Type 1diabetic patients (figure-I). Our study revealed that raised albumin excretion rate and blood pressure are concomitant phenomena in insulin dependent diabetic patients progressing to Microalbuminuria (p<0.001) (figure-II). When multiple logistic regression analysis was applied, glycaemic control, hypertension and duration of diabetes and was found to be strong predictors of Microalbuminuria/ diabetic nephropathy (Table-III).

DISCUSSION : In the present study, the mean duration of diabetes in the group A was 6.43±0.89 years while that in the group B was 2.79±0.33 years, rendering these results highly significant for the duration of diabetes (p<0.001). Our observations were consistent with the findings of V.Vishwanathan, et al [10] who found that the prevalence of microalbuminuria increased with the increasing duration of diabetes. When mean urinary albumin concentration (mg/L) was compared with the increasing duration of diabetes mellitus, it was seen that the degree of microalbuminuria increased significantly (p=0.001) with the increasing duration of diabetes mellitus. Our results support the findings of H.Moayeri et al[13], Krolewski et al[14] and A. Kofoed Enevoldsen et al[15] who observed an increased trend of urinary albumin concentration with increasing duration of diabetes.

In pediatric patients having age at onset up to 10 years, the mean urinary albumin concentration was 78±10.4 mg/L, in adolescent group having age at onset between 11-18 years was 130 ± 11.6 mg/L and the adult group with age at onset of more than 18 years was 121.4± 12 mg/L. This observation indicates that albumin excretion increases between the age of onset of 10 to 18 years but no further increase seen in adult life. Our findings were concordant with those of Krolewski et al [14], who suggested that the risk of persistent proteinuria is influenced by attained age. Moreover, in persons with onset of type 1 diabetes before the age of 10 years, nephropathy develops later than in those with onset after puberty and the risk of persistent proteinuria declines after the age of 35 years regardless of the duration of diabetes (Kofoed-Enevoldsen A et al)[15]. However, some previous studies indicated that the onset of microalbuminuria before puberty occurs only rarely and consequently screening for microalbuminuria should be recommended for children over 12 years of age [16-18]. There are only a few reports of diabetic children who develop diabetic nephropathy in prepubertal period [19,20].

The relationship of microalbuminuria with glycemic control was in concordance with the findings of Mulec H, et al [21] who studied the effect of metabolic control on the rate of decline in renal function in type 1 diabetes and reported that persistent hyperglycemia is a risk factor for diabetic nephropathy. Our study showed a statistically significant (p=0.001) parallel increase in the prevalence of microalbuminuria and the level of HbA_1C. These results were in concordance with those found by Diabetes Control and Complications Trial (DCCT) Research Group [22] that recommended the goal for glycemic control ideally is of HbA_1C level less than 7%. On the contrary, "Microalbuminuria Collaborative Study Group" of United Kingdom [23] reported that the likelihood of progression to clinical albuminuria was not associated with the HbA_1C concentration. According to this group, intensive diabetic therapy may improve the course of other complications such as retinopathy and neuropathy. Some of the mechanisms that link hyperglycemia to the functional and structural abnormalities of diabetic kidney disease include non enzymatic glycation of protein, activation of polyol pathway, activation of hexosamine pathway and increased intracellular accumulation of reactive oxygen species. All these biochemical pathways have been implicated in hyperglycemia-induced kidney damage.

Parving H.H, et al[24] and J. Michael, et al (1994)[25] showed that nephropathy and retinopathy almost co-existed. Presence of microalbuminuria and renal disease is an excellent predictor of the presence of retinopathy. Our study also concluded that as the degree of microalbuminuria increases, the involvement of retina increases in type 1 diabetic patients. Microangiopathy- whereby the basement membrane of the capillaries thickens, reducing the space in the capillaries, is believed to occur in retinal vessels as in glomerular capillaries, giving rise to retinopathy. However, according to Chavers B.M. et al [26], a marked discordance between retinopathy and nephropathy occurs as evidenced by normal urinary albumin excretion, low- level microalbuminuria and normal glomerular structural measures in patients with advanced retinopathy.

The association found between microalbuminuria and lipid profile in our study was in harmony with the findings of Vannini P et al [27] who found that clear disturbances of plasma lipoprotein take place with advancing renal disease. They also found increases in cholesterol, low density lipoprotein (LDL), triglycerides, very low density lipoprotein (VLDL) and decrease in high density lipoprotein (HDL). Oxidized and glycated lipoproteins are implicated in causing direct renal injury, and that apolipoproteins accumulate in the meantime leading to a more rapid decline in glomerular filtration rate and contributing directly to renal damage resulting in proteinuria. Endothelial dysfunction, abnormalities of the rennin-angiotensin system and widespread. Basement membrane defects are some of the proposed mechanisms linking renal and vascular diseases.

When the relationship of mean urinary albumin concentration was seen with hypertension, it was found that 32 % patients were normotensives with a mean urinary albumin concentration of 74.50±12.66 mg/dl

while the corresponding value for 68 % hypertensive patients was 134.11±26.34 mg/dl. The difference between the two means was statistically highly significant (p=0.001) leading us to the conclusion that raised albumin excretion rate and blood pressure are concomitant phenomena in insulin dependent diabetic patients progressing to microalbuminuria. H. Moayeri et al [13] also observed that hypertension were highly significant in microalbuminuric patients as compare to normoalbuminuric patients. Similar observations were made by U.K. prospective diabetes study group [28] according to which the control of blood pressure can reduce the development of nephropathy. Resting heart rate is easy measurable parameter with prognostic implications. [29]

However, our results were in contrast with those of V.Vishwanathan [10] who carried out a study on persistent microalbuminuria in south Indian subjects and could not depict hypertension in them.

CONCLUSION: We observed the relation of microalbuminuria with certain parameters. However a greater effort and a much larger study would be required to predict the safe glycaemic level below which there is no risk of microalbuminuria in type 1 diabetes. Early detection and control of the modifiable risk factors could lead to a reduction in the incidence of microalbuminuria thus nephropathy in patients of type 1 diabetes. As these patients have an onset of diabetes in the early part of their life, the prevention of microalbuminuria would definitely affect their quality of life. A careful management of risk factors such as by achieving euglycaemia, control of the serum lipid levels, retinopathy and hypertension can prevent or postpone the development on microalbuminuria.

REFERENCES:

1. Dennis L Kasper, Eugene Brunwald, Stephen Hauser, Dan Longo, Larry Jameson, & Anthony S Fauci Harrison. Harrison's principles of Internal Medicine 16 edition. Mc Grew Hills.2004.p.2152-53.
2. Luigi Gnudi et al In : John C Pickup and Gareth Williams Pickup. William's Textbook of diabetes 3rd edition.Wiley Blackwell. 2002.p 52.1-52.22.
3. Defronzo R.A. Diabetic nephropathy. In: Porte D, Sherwin R, eds. Ellenberg and Rifklin's diabetes mellitus. Sixth edition. New York. Mc Grew-Hill Companies.2002. 723-740.
4. Vats A., Deruberis F. Diabetic nephropathy. In: Sperling MA, editor. Type 1 diabetes, etiology and treatment.1st ed.Totowa, NJ. Human Press Inc.2003; 409-427.
5. Francis J., Rose S.J., Raafat F., Milford D.V. Early onset of diabetic nephropathy. Arch Dis Child. Dec.1977; 77: (6) 524-525.
6. Joner G., Brinchmann-Hansen O., Torres C.G., Hanssen K.F. A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian type 1 (insulin-dependent) diabetic patients. Diabetologia. Nov 1992; 35(11): 1049-1054
7. Bruno G, Pagano G. Low prevalence of microalbuminuria in young Italian insulin-dependent diabetic patients with short duration of disease: a population based study. Piedmont Study Group for Diabetes Epidemiology. Diabet Med. Oct1996; 13(10): 889-893

8. Patel K.L., Mhetras S.B., Varthakavi P.K. et al. Microalbuminuria in insulin dependent diabetes mellitus. J Assoc Physicians India.Jun1999; 47(6):589-595.
9. Boak M.A., Odink R.J., Delemarre-van de Waal H.A. Microalbuminuria as risk factor for nephropathy in children with insulin-dependent diabetes mellitus. Ned Tijdschr Geneeskd. Jul 1993; 137(27):1349-1352.
10. Vishwanathan V., Snehalatha C., Shina K., Ramachandran A. Persistent microalbuminuria in type 1 diabetic subjects in South India. J Assoc Physicians India. Oct 2002; 50: 1259-1261
11. Grenfell A. Management of nephropathy. In: pickup J.C, William G, eds. Textbook of diabetes 1997; 2nd edition. Oxford: Blackwell Sciences Ltd., p-54.1-54.19.
12. Sally M., Marshall. Clinical features and management of diabetic nephropathy. In: pickup J.C, William G, eds. Textbook of diabetes. 2003 Vol.2 and 3rd edition: p-53.2.
13. Moayeri H., Dalili H. Prevalence of microalbuminuria in Children and Adolescents with Diabetes Mellitus Type 1. Acta Medica Iranica. 2006; 44(2): 105-110.
14. Andrzej S. Krolewski et al. The changing natural history of nephropathy in type 1 Diabetes. Am J of Med.1985; 78:785-794
15. Kofoed-Enevoldsen A. et al. Declining incidence of persistent proteinuria in Type 1 (insulin dependent) diabetic patients in Denmark. Diabetes 1987; 36:205-209.
16. Mathiesen E.R., Saurbrey N., Hommel E., Parving H.H. Prevalence of microalbuminuria in children with type 1 (insulin dependent) diabetes mellitus. Diabetologia Sep 1986; 29(9): 640-643.
17. Dahlquist G., Rudberg S. The prevalence of microalbuminuria in children and adolescents and its relation to puberty. Acta Paediatr Scand. Sep 1987; 76(5): 795-800
18. Mortensen H.B., Marinelli K., Norgaard K. et al. A nationwide cross-sectional study of urinary albumin excretion rate, arterial blood pressure and blood glucose control in Danish children with type 1 diabetes mellitus. Danish Study Group of Diabetes in Childhood. Diabet Med. Dec 1990; 7(10): 887-897
19. DeClue T.J., Campos A. Diabetic nephropathy in a prepubertal diabetic females. Pediatr Endocrinol. Jan-Mar 1994;7(1):43-46.
20. Bayazit A.K., Yuksel B., Noyan A. et al. Early onset of diabetic nephropathy in a child type 1 diabetes mellitus. Turk J Pediatr. Jan-Mar 2003; 45(1): 55-58.
21. Mulec H., Blohme G. et al. The effect of metabolic control on rate of decline in renal function in IDDM with overt diabetic nephropathy. Nephrol Dial Transplant 1998; 13: 651-655.
22. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in Insulin Dependent Diabetes Mellitus. Engl. Med 1993; 329-977.
23. Microalbuminuria Collaborative Study Group. UK. Intensive therapy and progression to clinical albuminuria in patients with IDDM and microalbuminuria. BMJ 1995; 311:973-977.
24. Parving H.H., Hommel E. et al. Prevalence of microalbuminuria, arterial hypertension, retinopathy and nephropathy in patients with Insulin dependent diabetes. BMJ 1998; 299: 533-536.
25. Michael J., Carella et al. Early diabetic nephropathy. Archives of Internal Medicine. 1994; 154: 625-630.

26. Chavers B.M., Maller S.M., Ramsay R.C., Steffes M.W. Relationship between retinal and glomerular lesions in IDDM patients. Diabetes 1994; 43(3): 441-446.
27. Vannini P. et al. Lipid abnormalities in Insulin dependent diabetic patients with albuminuria. Diabetes Care 1984; 7: 151-154.
28. The UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macro vascular and micro vascular complications in Type 2 diabetes: UK-PDS 38. BMJ 1998; 317: 703-713.
29. Motilal C. Tayade, Nandkumar, B.Kulkarni , A comparative study of resting heart rate in smokers and nonsmokers , IJCRR , Vol.4 (22) ; 59-61

Table-I : Demographic profile of the Study Population

Parameters	(Group A; n=38)		(Group B; n=62)		t	p
	Mean	± SE	Mean	± SE		
Age (years)	27.84	1.83	25.51	1.27	1.04	0.48
Age at Onset (years)	21.40	1.76	22.72	1.27	0.611	0.65
Diabetic Duration (years)	6.43	0.89	2.79	0.33	4.22	<0.05*
BMI (kg/m^2)	21.05	0.76	21.46	0.64	0.418	0.73
W/H Ratio	0.88	0.01	0.88	0.01	-	NS

*statistically significant

Table-II : Biochemical parameters of the study population

Parameters	(Group A; n=38)		(Group B; n=62)		t	p
	Mean	± SE	Mean	± SE		
FBS (mg/dl)	203.45	12.17	165.28	7.26	2.72	<0.01*
HbA_1C (%)	0.08	0.003	0.06	0.001	6.66	<0.001*
TC (mg/dl)	181.63	6.35	165.63	2.10	2.35	0.02*
TG (mg/dl)	130.94	3.45	120.08	2.26	3.07	<0.005*
HDL (mg/dl)	57.53	2.73	72.56	1.91	4.55	<0.001*
LDL (mg/dl)	109.87	2.86	102.05	1.54	2.41	0.02*
VLDL (mg/dl)	30.64	1.24	26.08	1.49	2.40	0.02*

*statistically significant

Table-III: Microalbuminuria and its association with risk factors of Type-1 diabetes mellitus (Multiple logistic regression analysis)

Parameter	Odd's Ratio (OR)	Confidence Interval (95%CI)
Family History (+)	2.142	0.765-6.002
W/H Ratio	2.64	0.98-5.96
BMI (kg/m^2)	1.269	0.446-3.610

Conti….

Age at onset (years)	1.624	0.536-6.421
Duration of diabetes (years)	3.41	1.360-8.55
Fasting blood sugar (mg/dl)	3.491	1.138-10.70
Glycosylated Hb (%)	2.381	1.1-5.64
Total Cholesterol (mg/dl)	0.987	0.327-2.97
LDL Cholesterol (mg/dl)	1.8	0.47-6.82
HDL Cholesterol (mg/dl)	0.5714	0.099-3.27
TG (mg/dl)	1.527	0.54-4.27
VLDL Cholesterol (mg/dl)	1.563	0.53-4.60
Hypertension (mmHg)	5.087	2.139-12.101

FIG-I : Mean Urinary albumin concentration in relation to Retinopathy

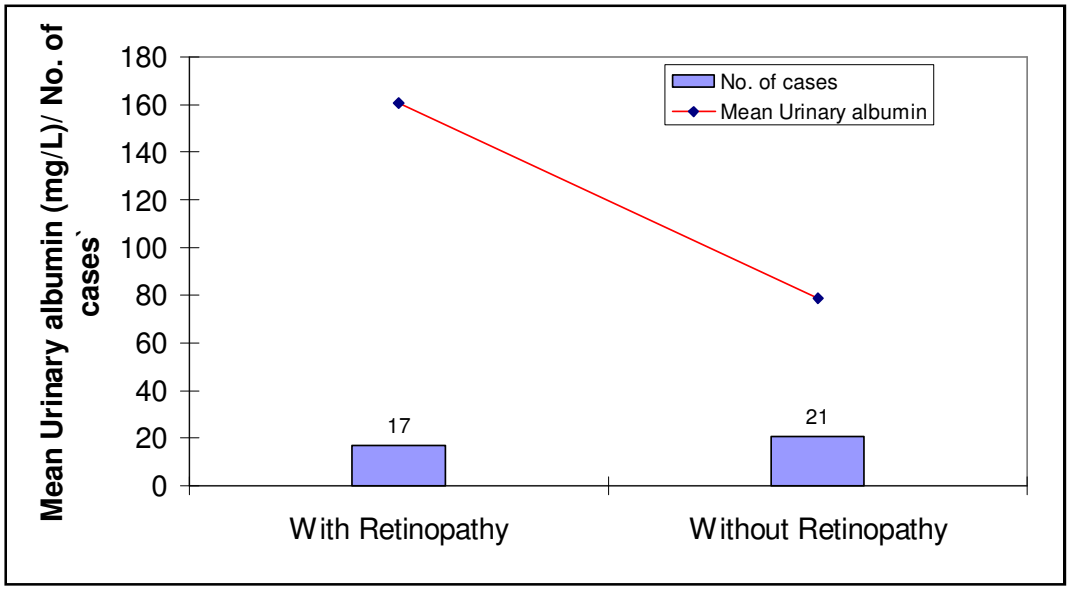
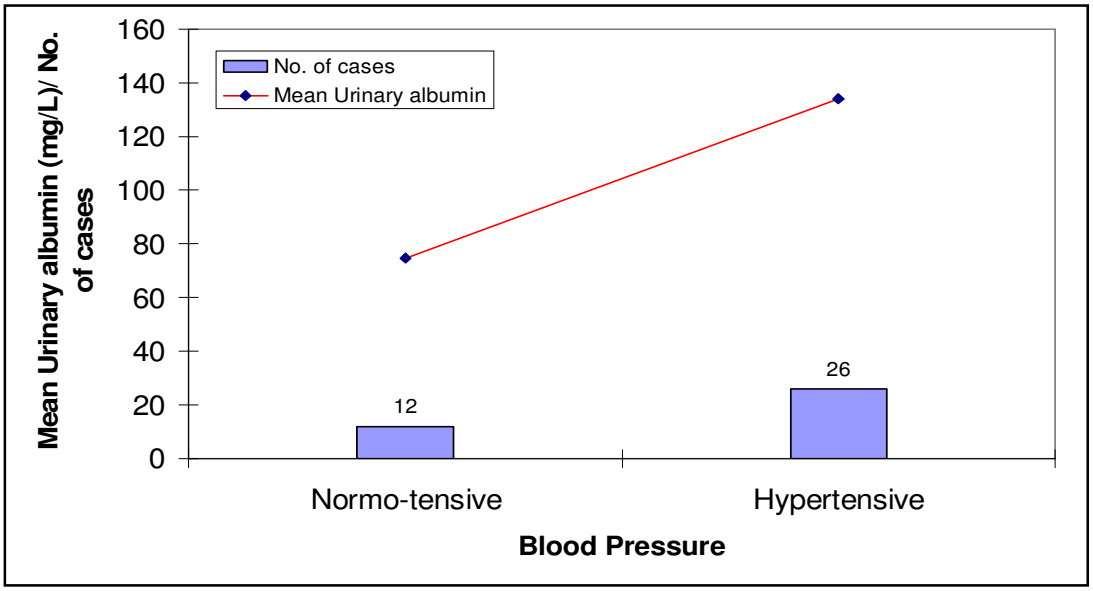


FIG-II : Mean Urinary albumin concentration in relation to Hypertension



Date of submission: 22 October 2012

Date of provisional acceptance: 10 November 2012

Date of Final acceptance: 28 February 2013

Date of Publication: 03 April 2013

Source of support: Nil; Conflict of Interest: Nil