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ORIGINAL RESEARCH ARTICLE

Reversal of Microalbuminuria A Causative Factor of Diabetic Nephropathy is Achieved with ACE Inhibitors than Strict Glycemic Control

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ABSTRACT

Aim: Microalbuminuria the after effect of diabetes mellitus if continues to progress can end up as diabetic nephropathy. It has been undisputedly agreed now, that when diabetes mellitus is diagnosed the complications will have already set in at a micro level. If we can intervene, identify and treat it early, the progress of the disease and worsening of it can be curtailed.

Study design: In this study 2 groups of patients with microalbuminuria the predictor of diabetic neuropathy were chosen and one group was ensured a strict glycemic control and the group were given ACE inhibitors along with strict glycemic control. The sample size was 50. The effect of both groups on reversal of microalbuminuria were studied after six months.

Results: The obtained results showed significant difference between group A and group B ($p<0.0001$) for the levels of microalbumin. Pre and post test within group B also showed significant difference ($p<0.0001$).

Conclusion: Microalbuminuria is the earliest clinically detectable stage of diabetic neuropathy. Providing only a strict glycemic control will not suffice to reverse the condition. ACE inhibitors delay the progress of microalbuminuria and also reverse the situation. Hence performing the test every six months should be done as a routine and if positive they should be given ACE inhibitor to avoid its progression to diabetic nephropathy.

Key words: Microalbuminuria, ACE inhibitors, Diabetic nephropathy.

INTRODUCTION

Diabetic nephropathy (DN) is one of the most serious complications of diabetes and the most common cause of end-stage renal failure. Diabetic kidney disease affects about 15 to 25% of type 1 diabetic and 30 to 40% of type 2 diabetic patients [1]. Features of early diabetic nephropathy changes are glomerular hyperfiltration, glomerular and renal hypertrophy, increased urinary albumin excretion (UAE), increased basement membrane thickness (BMT).

DN has been classically defined as increased protein excretion in urine. Early stage is characterized by a small increase in urinary albumin excretion (UAE), also called microalbuminuria or incipient DN. In most cases, proteinuria and decreased glomerular filtration rate (GFR) occur in parallel. Traditionally, GFR has been expected to decrease when proteinuria is established and not before. Microalbuminuria is the presence of small amount of albumin in urine, is the earliest known manifestation in diabetic nephropathy. Also called as “early diabetic nephropathy” or “incipient nephropathy” is the presence of albumin in the urine of 20 to 200 microgram/min (spot test) or 30 to 300 mg of albumin per 24 hours. Angiotensin II (AT II) stimulates matrix molecular synthesis and cell hypertrophy, also stimulates filtration of proteins across the glomerular capillary wall. Decreased AT II lowers systemic vascular resistance, reduces blood pressure, and decreases renal vascular resistance, thereby increasing glomerular filtration rate and Renal Blood Flow. ACE inhibitors (Angiotensin converting enzymes) decrease vascular resistance by antagonizing Angiotensin II – mediated vasoconstriction [2]. ACE inhibition retard glomerular basement membrane thickening [3] and tubular interstitial injury [4]. Also persistent

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hyperglycemia is a strong risk factor for DN [5] and causes the proliferation of mesangial cells and their matrix, as well as the thickening of the basement membrane.

Table 1: Diabetic nephropathy stages based on urinary albumin excretion

Stage	Urinary AER (microgm/min)	24 hour urinary AER (mg/24h)	Albumin/creatinine ratio.
Normoalbuminuria	<20	< 30	<0.02
Microalbuminuria	20 – 200	30 – 300	0.02 – 0.20
Macroalbuminuria	>200	>300	>0.20

Table 2: Natural history of diabetic nephropathy

Years	-3	0	3	10	15	19	22
GFRml/min	120	150	150	120	60	<10	<10
Creatinine mg%	1.0	0.8	0.8	1.0	>2	>10	>10
Urea mg%	15	10	10	15	>30	>100	>100
Stages	Pre diabetic	Onset of diabetes	Onset of glomerulo Sclerosis	Microalbuminuria	Onset of Proteinuria	Onset of Azotemia	ESRD(end stage renal disease)

At the time of diagnosis of diabetes, renal function and glomerular histology are normal. Within two to three years increased mesangial matrix and basement membrane thickening are observed. Renal function remains normal until 15 years, when proteinuria develops. This is an ominous sign and usually indicates advanced diabetic glomerulosclerosis[6]. Within five years after the onset of proteinuria, half of the patients have advanced to end stage renal disease (ESRD).

Studies suggest that only 30 to 45% of microalbuminuric patients will progress to proteinuria over 10 years of follow-up. In fact, some of them will present regression to normoalbuminuria. Independent of the role as a prognostic factor for macroalbuminuria, the presence of microalbuminuria, reflecting a state of generalized endothelial dysfunction, is a risk factor for cardiovascular disease and mortality. Hence the disease warrants an early assessment of renal parameters though patient is asymptomatic. Under such situation we have tried to assess the possibility of reversal of microalbumunuria when detected early by administering ACE inhibitors and also providing strict glycemic control and its response.

MATERIALS AND METHODS

The study was carried out after obtaining the necessary approvals from the Institutional Human Ethics Committee and Institutional Research Committee. The period of the study was six months. The study was done on two groups of patients. Samples of 25 numbers in each group, was taken accounting to a sample size of 50.

Group A

Microalbuminuria positive diabetic patients, who were given strict glycaemic control alone.

Group B

Microalbuminuria positive diabetic patients, who were given both strict glycemic control and ACE inhibitor

Parameters taken for analysis were

a) urine- microalbumin
b) urine – albumin/ creatinine ratio
c) HbA1c

Of the three parameters taken for the analysis “a and b” reflects the renal parameters. This helps us to identify the early renal pathology. This is treated as one group and is identified as group 1 parameters. The parameter “c” reflects the glycemic control. This helps us to identify the diabetic status of the individual. This is treated as another group and is identified as group 2 parameter.

The analysis of the parameters was done group wise in two set of samples that are taken.

The two set of samples taken are categorized as GROUP – A and GROUP – B. Both groups are compared based on the two set of group 1 and group 2 parameters for two periods as current month and sixth month.

The following method was adopted to select patients: Day – 1 procedure

Patient on day- 1 was subjected to certain basic tests such as

a) fasting blood glucose
b) post prandial blood glucose
c) Urine- routine

The reports were interpreted as following

IF - Fasting and (> 250mg %), Post prandial remains very high (> 400mg%)

HbA1c > 7

Urine- routine shows,Albumin and pus cells > 15 / HPF, Pus casts and leucocytes > 15 / HPF

The above reports indicates that the patients are not suitable for microalbumin assessment

If all the three tests ie fasting, post prandial, are within control and a normal urine routine then the microalbuminuria test[7] and the albumin – creatinine ratio[8] are done on the next day ie (day-2).

Group A:

Microalbuminuria positive diabetes patients are subjected to glycemic control alone.

A sample of 25 patients was selected and the

Glycemic control of HbA1c less than seven (< 7) is maintained.

Microalbumin in urine > 15 mg

Albumin/ creatinine ratio – 0.02 – 0.20

Microalbuminuria should be checked 6 months after the first time reading and interpreted. The results are to be compared with the group B

Group B

Micro albuminuria positive diabetic patients were subjected to glycemic control and treated with ACE inhibitors. A sample of 25 patients was selected. ACE inhibitors are given for 6 weeks and the microalbumin and albumin /creatinine ratio are assessed. If it does not attain the normal level then the dose of ACE inhibitors is increased. All parameters mentioned in the list should be checked after 6 months since first time reading was interpreted and analysed.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

a) Type 2 diabetic patients
b) All patients who are microalbumin positive after subjecting them to day 1 test

EXCLUSION CRITERIA

a) Exercise within 24 hours
b) Fever
c) Infection especially urinary tract infection
d) Congestive heart failure
e) Renal calculi
f) Marked hyperglycemia and marked hypertension.

A purposive sample with sample size of 50 of such patients was taken. The study was done on the patients after clearly explaining to them regarding the purpose of the study and getting the written informed consent which was made bilingual. This was done to both group A and group B patients. The statistical analysis was done with SPSS software. The comparison of two groups (group A and group B) were done using the statistical tool student's t test. Statistical probability (p) of $p < 0.05$ was considered to be significant.

RESULTS AND DATA ANALYSIS

The data collection was done after which the analysis was done as already mentioned and the results were obtained as follows.

Table 3: Statistical evaluation of the post test values (6th month) of Microalbumin in Group A and Group B

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Group – A Control (n = 25)	52.8	13.0	10.4	0.0001 *	Significant
Group – B Case (n = 25)	24.9	3.5			

* Highly significant; Values are ±SD

Table 4: Statistical evaluation of the post test values (6th month) of Albumin Creatinine Ratio in Group A and Group B

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Group – A Control (n = 25)	0.171	0.09	10.2	0.0001 *	Significant
Group – B Case (n = 25)	0.0801	0.008			

* Highly significant; Values are ±SD

Table 5: Statistical evaluation of the pre and post test values of Microalbumin in Group A

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Pre test value (0 Month) (n = 25)	34.6	10.8	- 5.39	0.0001 *	Significant
Post test Value (6^{th} Month) (n = 25)	52.8	13.0			

* Highly significant; Values are ±SD

Table 6: Stastistical evaluation of the pre and post test values of Albumin Creatinine Ratio in Group A

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Pre test Value (0 Month) (n = 25)	0.100	0.02	-7.24	0.0001 *	Significant
Post test Value (6^{th} Month) (n = 25)	0.171	0.09			

* Highly significant; Values are ±SD

Table 7: Stastistical evaluation of the pre and post test values of Microalbumin in Group B

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Pre test Value (0 Month) (n = 25)	75.5	8.63	27.5	0.0001 *	Significant
Post test Value (6^{th} Month) (n = 25)	24.9	3.5			

* Highly significant; Values are ±SD

Table 8: Stastistical evaluation of the pre and post test values of Albumin creatinine Ratio in Group B

Parameters	Mean Value	Standard deviation	T - Value	P - Value	Significance
Pre test Value (0 Month) (n = 25)	0.147	0.010	5.81	0.0001 *	Significant
Post test Value (6^{th} Month) (n = 25)	0.0801	0.008			

* Highly significant; Values are ±SD

DISCUSSION

The analysed data of the Group A and Group B for the microalbuminuria post six months was done, A significant difference in the microalbumin (p - <0.0001) was observed between the two groups. With individuals of group B registering a lower microalbumin than group A individuals clearly suggests that reversal of microalbumin is better with drugs like ACE inhibitor[9] than glycemic control (Table 3).

The analysed data of the group A and group B for the albumin creatinine ratio post six months was done With individuals of group B registering a lower albumin creatinine ratio than group A individuals clearly suggests that reversal of albumin creatinine ratio is better with drugs like ACE inhibitor than glycemic control (Table 4).

The analysed data of pre and post test within group A for microalbumin was done. The data obtained between the pre and post test values within the group A are as follows, the pretest value was 34.6 ± 10.8 and the post test value was 52.8 ± 13.0. A significant difference in the microalbumin (p - <0.0001) was observed between the two values. The post test value of microalbumin is higher than the pretest value thereby suggesting that the reversal of microalbumin is not possible with glycemic control alone (Table 5).

The analysed data of pre and post test within group A for albumin creatinine ratio was done The data obtained between the pre and post test values within the group A are as follows, the pretest value was 0.100 ± 0.02 and the post test value was 0.171 ± 0.09. A significant difference in the albumin creatinine ratio (p - <0.0001) was observed between the two values. The post test value of albumin creatinine ratio is higher than the pretest value thereby suggesting that the reversal of albumin creatinine ratio is not possible with glycemic control alone (Table 6).

The analysed data of pre and post test within group B for microalbumin was done. The data obtained between the pre and post test values within the group B are as follows, the pretest value was 75.5 ± 8.63 and the post test value was 24.7 ± 3.5. A significant difference in the microalbumin (p - <0.0001) was observed between the two values. The post test value of microalbumin is lower than the pretest value thereby suggesting that the reversal of microalbumin was possible with ACE inhibitor[10] that was administered during the six months period (Table 7).

The analysed data of pre and post test within group B for albumin creatinine ratio was done.The data obtained between the pre and post test values within the group B are as follows, the pretest value was 0.147 ± 0.010 and the post test value was 0.0801 ± 0.008. A significant difference in the albumin creatinine ratio (p - <0.0001) was observed between the two values. The post test value of albumin creatinine ratio is lower than the

pretest value thereby suggesting that the reversal of albumin creatinine ratio was possible with ACE inhibitor that was administered during the six months period (Table 8).

CONCLUSION

Microalbuminuria is the earliest clinically detectable stage of diabetic nephropathy. The ACE inhibitors play a greater role in controlling the progress to clinical nephropathy [11] and also reversal of microalbumin [12] level than glycemic control alone. Strippoli GF. *et al.* [13] have said that ACE inhibitors delay microalbuminuria in diabetes without nephropathy and reduce mortality in diabetic nephropathy. Significant reduction in the risk for developing microalbuminuria in patients who had diabetes with no nephropathy was demonstrated for ACE inhibitors

- Perform an annual test[14] for the presence of microalbuminia in 1) type 1 diabetic patients who have had diabetes >5 years and 2) all type 2 diabetic patients starting at diagnosis.
- In the treatment of albuminuria/nephropathy ACE inhibitors can be used:
    - In hypertensive type 1 diabetic patients with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.
    - In hypertensive type 2 diabetic patients with microalbuminuria, ACE inhibitors have been shown to delay the progression to macroalbuminuria.
- Hence ACE inhibitor should be used along with glycemic control and if the beneficial effect of the ACE inhibitor is observed, therapy should be continued for life, since withdrawal of the ACE inhibitor will lead to a return of microalbuminuria[15].
- American diabetes association (ADA) now recommends ACE inhibitor for all type I and type II diabetes mellitus patients with microalbuminuria even if they are normotensive.

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