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EFFECTS OF N-ACETYL CYSTEINE ON PROTEINURIA IN TYPE 2 DIABETIC PATIENTS WITH DIABETIC NEPHROPATHY

Dr. Hossain Muhammad Mustafijur Rahman[1*], Prof. Dr. Md. Nizamuddin Chowdhury[2], Prof. Dr. Md. Nazrul Islam[3], Dr. Md. Aminul Islam[4], Dr. G. M. Hafizur Rahman[5], Dr. Faruque Ahmed[6], Dr. Md. Tanvir Rahman[7], Dr. Nahid Afrin[8] and Dr. Sheikh Mohammad Samsuzzaman[9]

[1]Assistant Professor (Nephrology), Dhaka Medical College, Dhaka, Bangladesh.
[2]Professor & Ex-Head, Department of Nephrology, Dhaka Medical College & Hospital, Dhaka, Bangladesh.
[3]Professor and Head, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh.
[4]Transplant Co-Ordinator, (Nephrology), Dhaka Medical College Hospital, Dhaka, Bangladesh.
[5]Assistant Professor, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh.
[6]Assistant Professor (Nephrology), Sheikh Russel Gastro Liver Institute and Hospital, Dhaka, Bangladesh.
[7]Nephrologist, United Hospital Ltd, Dhaka, Bangladesh.
[8]Nephrologist, National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh.
[9]Assistant Professor, Medicine, Sir Salimullah Medical College, Mitford Hospital, Dhaka, Bangladesh.

***Corresponding Author: Dr. Hossain Muhammad Mustafijur Rahman**

Assistant Professor (Nephrology), Dhaka Medical College, Dhaka, Bangladesh.

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ABSTRACT

Background: Diabetic nephropathy is one of the leading cause of ESRD. Limited drugs are available to reduce proteinuria in diabetic nephropathy. It is thought that N-acetyl Cysteine (NAC) has anti-proteinuric effect.**Objective:** To assess the effect of N-acetyl Cysteine (NAC) on proteinuria in type 2 diabetic patients with diabetic nephropathy. **Methods**: This is a prospective interventional study and conducted at the Department of Nephrology in DMCH. Total 65 patients were included in the study and they were divided into two groups named control (Group I, n = 33) and intervention group (Group II, n = 32). Then Group II was given NAC (oral 600mg twice daily) for two months in addition to standard medication and Group I was only on proper doses of standard medication. Data were collected at day 0 and at day 60. Comparison of the two groups were done to find out the effect of N-acetyl Cysteine.**Results:** At the beginning (Day 0), mean albumin/creatinine ratio (ACR) in Group I and Group II were 405.80±488.89 SD and 501±568.75 SD respectively. A significant reduction of ACR value was noted in Group II after intervention (p value <0.001). But in Group Ithere was mild rise in ACR at Day 60 which was insignificant (p value 0.51). Whereas, a significant reduction of protein creatinine ratio (PCR) was noted in both Group I (p < 0.04) and Group II (0.001) at Day 60. The reduction in Group II was highly significant. **Conclusion:** NAC significantly reduces proteinuria in diabetic nephropathy patients.

KEYWORDS: Anti-proteinuric drug, N-Acetyl Cysteine (NAC), Drug treatment of diabetic nephropathy.

INTRODUCTION

Around 347 million people have been suffering from Diabetes Mellitus worldwide and this number is expected to increase to 430 million by 2030.[1] Diabetic nephropathy is characterized by an increased urinary albumin excretion in the absence of other renal diseases.[2] Overt nephropathy is more common in type-2 diabetes than with type-I.[3] Progression from micro - albuminuria to overt nephropathy occurs in 5–20% patients, which is more frequent in Asian or African descent.[2]

The pathophysiology of diabetic nephropathy is poorly understood. Metabolic alterations (hyperglycaemia and possibly hyperlipidaemia) and haemodynamic alterations (systemic and glomerular hypertension) and influence of inflammation, endothelial dysfunction and oxidative stress, are possible underlying causes. Therefore, current treatment modalities relies on the nephroprotective, antiproteinuric and antihypertensive effects of renin–angiotensin system (RAS) blockade in addition to optimized metabolic and blood pressure control.[4]

N-acetyl Cysteine (NAC), a thiol, is a pharmacological precursor of L-cysteine. When it is administered in reduced form, it rapidly increases systemic levels of cysteine that in turn vasodilates and activates guanylate cyclase more potently than NO and act as important stable reservoirs of NO.[5]

For that reason, NAC is generally being used as an antioxidant, vasodilator and insulin regulatory agent.[5] Various studies have been conducted on the beneficial effects of antioxidant drugs, such as NAC, slowing of CKD progression.[6] Considering the potential benefits of both this phenomenon in type 2 diabetic individual, the study was designed to assess the effects of N-acetyl Cysteine on proteinuria in type 2 diabetic patients with diabetic nephropathy.

METHODOLOGY

It was a prospective interventional case control study. Data were collected from the Department of Nephrology, Dhaka Medical College Hospital, Dhaka. This study was conducted for a period of 1 year, from June 2016 to May 2017. Diabetic patients with diabetic nephropathy attending in nephrology OPD or nephrology ward at DMCH were included in the study according to inclusion and exclusion criteria.

All of them were getting ACEI or ARB at maximum possible dose as well as standard anti- diabetic agents with well controlled blood pressure and blood sugar for more than 2 months. Those who had liver disease (SGPT > 2times), bradycardia, asthma, COPD, History of hypersensitivity to N-acetyle Cystein, unwanted or intolerable adverse effects of NAC during use of the drug, pregnancy, active peptic ulcer, eGFR< 15ml/min were excluded from the study. Non-probability purposive consecutive sampling method was used to select sample population. Total 65 patients were included in the study and they were divided into two groups named control group (Group I, n = 33) and intervention group (Group II, n = 32). Both groups were age matched.

A questionnaire was prepared considering key variables like demographic data, clinical presentation, clinical findings, predisposing factors, investigations. Every patient was gone through detailed history taking and physical examination. Patients blood and urine were collected for laboratory analysis.

Patients were randomly assigned according to systematic random sampling technique into a Group I and Group II. Patients of Group II were received NAC (600 mg every 12 hours orally) for 2 months along with standard medications. Patients of the Group I were received only standard medications. The dosage of anti-hypertensive, anti-diabetic agents, lipid lowering agents, and antiplatelet drugs were continued and adjusted according to the individual patient's clinical and biochemical parameters.

Statistical analysis was done by Statistical Package for Social Science (SPSS) version 20 (SPSS Inc., Chicago, Illinois, USA). The difference between groups were analyzed by independent sample t-test, paired t-test or Mann-Whitney U test when necessary. Probability value of less than 0.05 was considered as significant.

RESULTS

Table 1. Mean, minimum and maximum age of Group I (n=33) and Group II (n=32).

	Group	Mean±SD	Maximum	Minimum	P value*
Age (years)	I (n=33)	57.45±7.02	71	42	0.78
	II (n=32)	57.81±8.09	75	45	
***Independent samples t test was used**					

Total 65 patients of this study were divided into two groups randomly. Group I consisted of 33 and Group II consisted of 32 patients. Mean age of Group I and Group II were 57.45±7.02 and 57.81±8.09 respectively. This difference was not statistically significant. (Table 1).

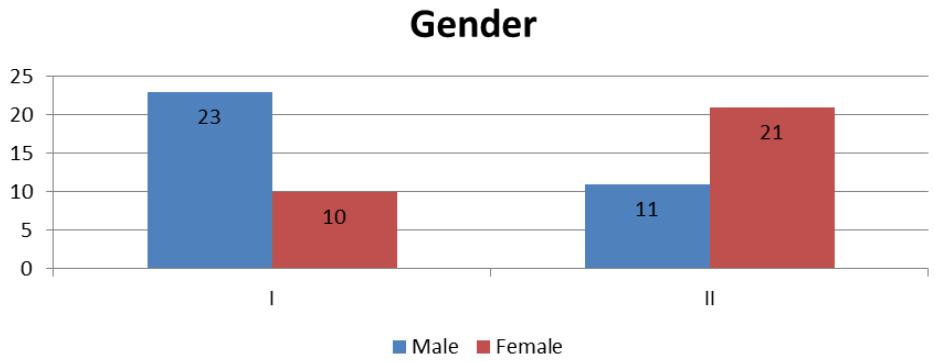

Figure: 1. Distribution of patients according to gender (Group I = 33 and group II = 32).

Total 34 male (52.3%) and 31 female (47.7%) were enrolled in this study. Out of 33 patients in Group I 23 were male (67.5%) and 10 patients were female (32.3%) and out of 32 patients in Group II 11 patients were male (32.4%) and 21 patients were female (67.7%). (Figure 1)

Table: 2. Comparison of some clinical variables of Group I (n = 33) and Group II (n = 32) at day 0.

	Group	Mean±SD	P value*
Duration of DM (months)	I (n=33)	12.24±3.03	0.337
	II (n=32)	13.28±5.25	
Systolic blood pressure (mmHg)	I (n=33)	129.39±12.03	0.004
	II (n=32)	138.59±13.02	
Diastolic blood pressure (mmHg)	I (n=33)	81.66±8.06	0.843
	II (n=32)	82.03±6.58	
BMI (kg/m^2)	I (n=33)	23.86±2.44	0.086
	II (n=32)	23.81±2.95	
***Independent samples t test was used**			

Group I had higher mean duration of DM (13.28±5.25) than that of Group II (12.24±3.03) though the difference was statistically insignificant (p=0.337). Mean systolic blood pressure of Group II (138.59±13.02 mm of Hg) was significantly higher than that of the Group I (129.39±12.03mm of Hg) with a p value of 0.004. Mean diastolic blood pressure and mean body mass index were similar in both groups. (Table 2).

Table 3. Comparison of some biochemical parametres between Group I (n= 33) and Group II (n =32) at Day 0.

	Group	Mean	±Std. Deviation	P value
FBS	I (n=33)	6.73	±0.88	0.07*
	II (n=32)	6.31	±0.97	
PPBS	I (n=33)	8.98	±1.10	0.33*
	II (n=32)	8.72	±1.08	
HbA1C	I (n=33)	6.66	±0.49	0.93*
	II (n=32)	6.67	±0.54	
Creatinine	I (n=33)	1.50	±0.29	0.25**
	II (n=32)	1.63	±0.42	
e-GFR	I (n=33)	48.38	±10.83	0.03**
	II (n=32)	41.88	±13.79	
*** Independent samples *t* test was used** **** Independent samples Mann-Whitney U test was used**				

There was no significant difference between mean values of fasting blood sugar, post-prandial blood sugar, HbA1c and serum creatinine between Group I and Group II. But significant difference was noted in distribution of eGFR across groups (p value 0.03). (Table 3).

Table 4. Comparison of ACR (Albumin Creatinine Ratio) and PCR (Protein Creatinine Ratio) between Group I (n=33) and Group II. (n=32) at Day 0.

	Group	Mean	Std. Deviation	P value*
ACR	I (n=33)	405.80	±488.89	0.61
	II (n=32)	501.76	±568.75	
PCR	I (n=33)	870.05	±493.41	0.80
	II (n=32)	934.53	±562.47	
*** Independent samples Mann-Whitney U test was used**				

Mean ACR in Group I and Group II were 405.80±488.89 and 501±568.75 at Day 0. Difference in distribution of ACR between two groups were not significant (p value - 0.61). Mean PCR in Group I and II were 870.05±493.41 and 934.53±562.47 at Day 0. Distribution of PCR across two groups were similar (p value 0.80). (Table 4).

Table 5: Comparison between Day 0 and at Day 60 values of some clinical variables in Group I and Group II.

	Group I (n= 33)			Group II (n=32)		
Clinical Variables	**At day 0**	**At day 60**		**At day 0**	**At day 60**	
	Mean ±SD	Mean ±SD	***p* value**	Mean ±SD	Mean ±SD	***p* value**
BMI(kg/m^2)[a]	23.86 ±2.44	23.94 ±2.36	**0.11**	23.81 ±2.95	23.72 ±2.85	**0.07**
Systolic BP (mmHg)[a]	129.39 ±12.03	128.78 ±9.18	**0.69**	138.59 ±13.02	134.68 ±6.59	**0.07**
Diastolic BP (mmHg)[a]	81.66 ±8.06	80.60 ±7.04	**0.40**	82.03 ±6.58	82.18 ±5.81	**0.89**
[a] Paired Sample T test						

No significant change of BMI, systolic BP and diastolic BP was noted in both Group I and Group II, when Day 0 values were compared with Day 60 values. (Table 5).

Table 6: Comparison between Day 0 and Day 60 values of some biochemical variables in Group I (n=33) and Group II (n=32).

	Group I (n= 33)			Group II (n=32)		
Biochemical variable	**At day 0**	**At 60 day**		**At day 0**	**At 60 day**	
	Mean ±SD	Mean ±SD	**P value**	Mean ±SD	Mean ±SD	**P value**
FBS (mmol/l)[a]	6.72 ±0.88	5.97 ±0.72	<0.001	6.30 ±0.96	6.41 ±0.72	0.49
PPBS(mmol/l)[a]	8.98 ±1.10	8.65 ±0.99	0.08	8.71 ±1.08	8.65 ±0.86	0.62
HbA1C[a]	6.65 ±0.48	6.61 ±0.49	0.52	6.67 ±0.54	6.67 ±0.42	1.0
Creatinine(mg/dl)[b]	1.50 ±0.29	1.47 ±0.31	0.74	1.63 ±0.41	1.59 ±0.35	0.09
eGFR[b]	48.38 ±10.82	49.40 ±11.78	0.84	41.87 ±13.79	41.89 ±11.61	0.96
[a] Paired Sample T test [b] Related Samples Wilcoxon Signed Rank Test						

No significant change was noted in PPBS(Post Prandial Blood Sugar), HbA1c, Creatinine and eGFR(estimated Glomerular Filtration Rate) values in Group I and Group II, when Day 0 values were compared with Day 60 values. Although a significant change in FBS(Fasting Blood Sugar) was observed in Group I (p value <0.001). (Table 6).

Table 7: Comparison between Day 0 and Day 60 values of ACR and PCR in Group I (n=33) and Group II (n=32).

	Group I (n= 33)			Group II (n=32)		
	At 0 day	**At 60 day**		**At 0 day**	**At 60 day**	
	Mean ±SD	Mean ±SD	**P value**	Mean ±SD	Mean ±SD	**P value**
ACR[a]	405.80 ±488.85	406.02 ±520.32	0.51	501.76 ±568.75	377.39 ±407.62	<0.001
PCR[a]	870.04 ±493.41	826 ±554	0.04	934.53 ±562.75	688.88 ±400.29	<0.001
[a] Related Samples Wilcoxon Signed Rank Test						

A significant reduction of ACR was noted in Group II after intervention (p value <0.001). But there was mild rise in ACR at Day 60 in Group I which was insignificant (p value 0.51). On the other hand, a significant reduction of PCR was noted in Group I at Day 60 (p value <0.04), but the reduction in Group II was highly significant (p value <0.001).(Table 7)

DISCUSSION

Total 65 diabetic nephropathy patients were enrolled in this study. Control group (Group I) was received standard treatment whereas intervention group (Group II) was received N-acetyl cysteine (NAC) in addition to the standard treatment. Baseline investigations were done in both groups including ACR and PCR to determine the outcome of the intervention (NAC 600mg twice daily for 2 months orally). These two groups were age matched **(Table 1)** but not matched in gender **(Figure 1).**

Shen Y et al. found that female gender had been associated with the development of nephropathy in diabetes and its progression in his study.[8] As there were more female participants in the intervention group in our study so it can be assumed that study result would not be altered by this mismatch rather study result could have been more significant if the groups were gender matched.

It is well established that duration of DM has important role in development of complications in both well controlled and poorly controlled state (Gross et al, 2005). Though, in this study, patients of Group II had higher mean duration of DM (13.28±5.25 SD) than that of Group I (12.24±3.03 SD), the difference was not statistically significant (p =0.337>.05). So the mean duration of DM would not make any difference in the outcome of control and intervention group.

At day 0 mean systolic blood pressure of Group I and Group II were 129.39±12.03 and 138.59±13.02; mean diastolic blood pressure were 81.66±8.06 and 82.03±6.58 and BMI were 23.86±2.44 and 23.81±2.95 respectively. At day 60 mean systolic blood pressure of Group I and Group II were 128.78±9.18 and 134.68±6.59; mean diastolic blood pressure were 80.60±7.04 and 82.18±5.81 and BMI were 23.94±2.36 and 23.72±2.85 respectively. At day 0, there was statistically significant difference of only SBP between Group I and Group II (p=0.004<.05**) (Table 2)**. There was statistically insignificant difference of DBP and BMI between Group I and Group II. 'Paired sample-t test' analysis showed no statistically significant changes of SBP, DBP and BMI (Table 4) during study period.

Though study participants were on regular medications and diet, the insignificant change of these parameters may be due to limited effect of NAC on them which is supported by 'The effect of N- acetylcysteine on blood pressure and markers of cardiovascular risk in non-diabetic patients with chronic kidney disease: a placebo-controlled, randomized, cross-over study' by Renke et al., (2009).[10]

Study participants were also assessed based on several biochemical parameters including fasting blood sugar (FBS), post-prandial blood sugar (PPBG), HbA1c and serum creatinine between Group I and Group II before starting intervention (NAC)(At Day 0). No significant changes were noted in PPBS, HbA1c, creatinine and eGFR values of both Group I and Group II, when Day 0 values were compared with Day 60 values. Although a significant change in FBS was observed in Group I but it would not affect the study result as it was at the control end of the study.

CONCLUSION

In this study it was found that N-acetyl Cysteine had positive effect on reduction of proteinuria in diabetic nephropathy.

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