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COMPARATIVE ANALYSIS ON RENAL FUNCTIONS IN BOTH INTERVENTION AND CONTROL GROUP AFTER ADMINISTRATION OF DOXYCYCLINE

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ABSTRACT

Background: Diabetic nephropathy is one of the leading causes of ESRD. Activity of matrix metalloproteinases (MMPs), the enzymes primarily responsible for the deposition of extracellular matrix proteins, contributes to the pathogenesis of diabetic proteinuria. Doxycycline, a potent nonselective MMPs inhibitor, reduce proteinuria in diabetic patients. **Objective:** In this study our main goal is tocompare on renal functions, especially proteinuria in both intervention and control group after administration of Doxycycline. **Method:** This prospective interventional study was conducted at the Department of Nephrology in DMCH.The study included 60 clinically proven adult patients of DN. All patients were on optimal doses of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for 2 months before the study. The patients were divided into two groups named control (group I, n = 30) and intervention group (group II, n = 30). Control group patients were maintained on optimal doses of ACEIs or ARBs, whereas intervention group patients received Doxycycline (100 mg/day) for a period of 3 months in addition to ACEIs or ARBs. Data were collected at month 0 and at month 1 at month 3. **Results:** Renal parameters were assessed at the beginning of the study, at month 1, at month 3. All renal parameters remained unaltered during the study in both groups. However, proteinuria showed improvement. The mean basal levels of 24 hours proteinuria was 2.2 ± 1.3g/day for Group I and 2.7 ± 1.42 g/day for Group II. P value is not significant in both group at baseline (p=0.2). Adequate glycemic control was achieved with insulin, oral hypoglycemic agents or both in all the patients. It reduced to 2.0 ± 1.2g/day for Group I and 2.5± 1.3g/day for Group II, at the end of 1 month. At the end of 3 months, a significant decline of proteinuria was observed in both the groups. In Group I it had a mean of 1.95 ± 1.2g/day, whereas it was 1.25± 0.78g/day in Group II. A statistically significant difference existed between the control and intervention groups ($p < 0.05$), at 3 months. **Conclusion:** In this study we can conclude that Doxycycline treatment in diabetic patients is capable of preventing progression of DN, instead of simply influencing one of its surrogate end points, albuminuria. Further long-term multicentric trials are required to determine the benefits of doxycycline in patients of DN.

KEYWORDS: Doxycycline, diabetic nephropathy, Proteinuria, renal functions.

INTRODUCTION

The prevalence of diabetes mellitus has reached an epidemic proportion. Worldwide, around 347 million people have the disease and this number is expected to increase to 430 million by 2030.[1] And the biggest share comes from developing part of the world. Recent estimates by the International Diabetes Federation (IDF), stated that, SEA region (India, Sri Lanka, Bangladesh, Bhutan, Mauritius and Maldives), is home to more than 72 million adults with diabetes in 2013 and is expected to exceed 123 million in 2035. Among them nearly 95% of having type 2 diabetes (T2DM).[2,3]Diabetic nephropathy (DN), is one of the leading causes of ESRD worldwide. The risk of nephropathy is strongly determined by polygenetic factors. The risk for development of DN is equal in type 1 and type 2 diabetes, and 30% to 40% of patients with type 1 or type 2 diabetes ultimately develops nephropathy.[4,5,6]

It is defined by increased urinary albumin excretion in the absence of other renal diseases [Gross et al., 2005].[5] Diabetic nephropathy has been classically defined by the presence of proteinuria >0.3 g/24 h.[7]

T2DM is associated with substantially increased risk of premature death — a risk that is primarily focused on those with nephropathy. For T2DM without kidney disease, this is 11.5%. For T2DM with kidney disease, this rises to an astonishing 31.1%, representing an absolute risk difference with the reference group of 23.4% (adjusted for demographics, smoking, and BP).[8]

Proteinuria increases mortality and morbidity rate in these patients.[9]

Reduction in albuminuria levels may slow progression of diabetic kidney disease and improve clinical outcomes, even in normotensive patients; therefore, albuminuria may be identified as a target for treatment in diabetic kidney disease (AJKD, 2007).[10] The remodeling and excess deposition of ECM could be attenuated by Doxycycline due to its property of MMP inhibition.[11]

The role of Doxycycline in decreasing proteinuria in patients with DN is still largely experimental. Only a few human studies have shown preliminary short-term results. The present study therefore tries to find out if Doxycycline has got any role in decreasing proteinuria in patients with DN.

Objective

General objective

- To compare on renal functions in both intervention and control group after administration of doxycycline.

Specific objective

- To assess the level of 24 hours proteinuria, in control group and intervention group at baseline, at end of 1st month and at the end of 3rd month
- To assess the level of serum creatinine, e-GFR in control group and intervention group at baseline and at the end of 3rd month
- To assess antiproteinuric effect of Doxycycline in Diabetic Nephropathy patients

METHODOLOGY

Type of study	**Prospective study**
Place of study	Department of Nephrology, Dhaka Medical College Hospital, Dhaka
Study period	January 2017 to July 2018.
Study population	Total 60patients were selected in two groups. Group I consisted of 30 control and group II consisted of 30 intervention. Patients of Type 2 DM with clinically proven diabetic nephropathy attending in Nephrology department in DMCH.
Sampling technique	Non-probability purposive sampling method

Inclusion criteria

- Adult patients (>18 years) with type 2 DM
- Patients with overt proteinuria (>500 mg/24 hr)
- All patients had to be optimal doses of ACEIs or ARBs for at least 2 months before enrollment.

Exclusion criteria

- History of hypersensitivity to tetracycline derivatives like doxycycline, minocycline.
- Hepatic dysfunction (transaminase levels greater than twice the upper limit of normal
- Uncontrolled Hypertension (blood pressure > 150/90 mm Hg)
- Poorly controlled diabetes
- e-GFR< 15ml/min/1.73m2 (MDRD)

Procedure of data collection

A questionnaire was prepared considering key variables like demographic data, clinical presentation, clinical findings, predisposing factors, investigations, were collected which was verified by the guide and the data were collected by the researcher himself. Every patient was gone through detailed history taking and physical examination- special attention to any H/O drug allergy. Patient´s blood and urine were collected for laboratory analysis.

Patients were purposively selected into a control group and a intervention group. Intervention group patients were received Doxycycline (100 mg daily orally) for 3 months. Patients of the control group were receiving their routine 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 condition.

All the intervention group patient were clinically assessed at 1st month of starting Doxycycline for adverse effect of Doxycycline. Both intervention group and control group patient were assessed clinically and biochemically at 1 and 3 months of treatment. Clinical and biochemical findings of control group and intervention group were compared with each other. All patients who took Doxycycline developed no major side-effect during study period. After 3 months Doxycycline stopped and conventional treatment were continued. Aany adverse events considered to be related to the use of Doxycycline were recorded during the follow-up assessment. For serious adverse events, Doxycycline therapy were discontinued and managed accordingly.

Statistical analysis

After collecting the data, it was checked and rechecked for omission, inconsistencies and improbabilities. After

cleaning the data it was edited, coded and entered into the computer. Statistical analysis of the study was be done by computer software device as the Statistical Package for Social Science (SPSS) version 20 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as means ± standard deviation, and categorical variables as frequencies and proportions. The differences between groups were analyzed by independent sample t-test, paired t-test, Wilcoxon Signed Ranktest when necessary. Statistical significance will be assumed when the probability value were less than 0.05

RESULTS

Table I: Some baseline parameters in group I and group II.

	Group I (n=30)	Group II (n=30)	p-value
Age (years)			
Mean ± SD	55.6 ± 10	54.7 ± 9.5	0.94
Gender			
Male	18(56.7%)	16 (53.3%)	0.36
Female	12(53.3%)	14 (46.7%)	
BMI *(kg/m^2)	23.86±2.44	23.81±2.95	0.08
Duration of DM**			
<10 years	9(30%)	12(40%)	0.13
>10 years	21(70%)	18(60%)	

BMI*:Body mass index **; DM**** : Diabetes mellitus.

Independent samples t test was used

Table I shows Mean age of control group and intervention group were 55.60±10 and 54.7± 9.5 respectively, This difference was not statistically significant. No significant difference of BMI in both groups. Male was more than female but difference was not statistically significant. Most patients have duration of DM more than 10 years.

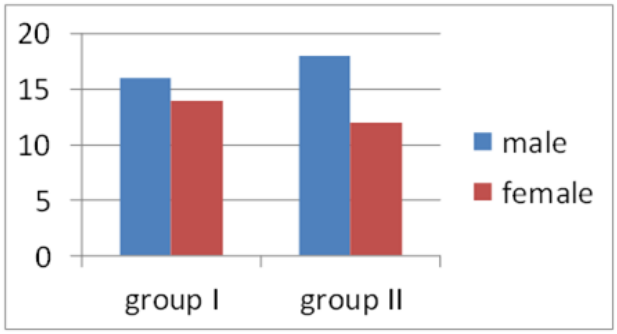

Figure I. Bar diagram showing distribution of patients according to gender (Group I = 30 and group II = 30) Total 34 male (56.7 %) and 26 female (43.3%) were enrolled in this study. Out of 30 patients in group I 18 were male (56.7%) and 12 patients were female (43.3%) and out of 30 patients in group II 16 patients were male (53.3 %) and 14 patients were female (46.7%).

Table II : Some baseline parameter of both group I and group II.

Baseline parameter	group I	group II
ACEI*	11**(**27%)	9(30%)
ARB **	19(63%)	21(70%)
Hypertension	30(100%)	30(100%)
OHA ^	8(27%)9(30%)	
Insulin	12(40%)	12(40%)
Both(OHA, insulin)	10(33%)	9(30%)

ACEI*: angiotensin-converting enzyme inhibitor**, ARB**:** angiotensin receptor blocker **OHA^:** oral hypoglycemic drug.

This table shows, group I and group II receiving ACEI 11(27%), 9(30%) and ARB 19(63%), 21(70%) respectively. Hypertension is equal in both groups. Among anti-diabetic drug insulin was most commonly using drug in both groups.

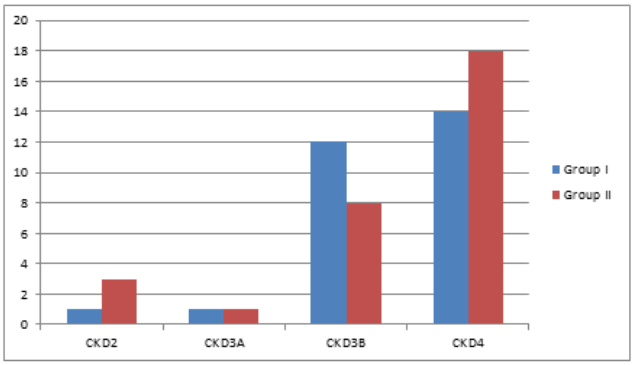

Figure II: Bar diagram showing distribution of patients according to stages of CKD (Group I = 30 and Group II = 30) Among distribution of CKD patients control group I CKD stage 2 was 1(3.3%), CKD stage 3A 1(3.3%), CKD stage 3B 12(40%),CKD stage 4 14(46.7%), intervention group II CKD stage 2 was 3(10%), CKD stage 3A 1(3.3%),CKD stage 3B 8(26.6%),CKD stage 4 18(60%). Both groups were similar in distribution.

Table III : Comparison of baseline clinical parameter of between group I and group II.

Clinical parameter	group I	group II	p-value
SBP* (mm Hg)	131±6.6	131±7.7	0.4
DBP (mm Hg)**	78±4.7	79±7.2	0.9

Retinopathy

NPDR^6(20 %)	7(23.3%)	
PDR ^^	18(60%)	16(53.3%)

Table III shows baseline systolic and diastolic blood pressure in both groups. Systolic blood pressure in group I and group II is 131± 6.6 and 131± 7.7 mm Hg respectively and diastolic blood pressure in group I and group II is 78± 4.7 and 79± 7.2 mm Hg respectively and is there was no significant difference in both groups. Majority patients has retinopathy in both groups.

Table IV: Comparison between pre-intervention and post intervention values of some baseline biochemical variables in both group I and group II.

Biochemical variable	Group I (n= 30)			Group II (n=30)		
	At 0 month	**At 3rd month**		**At 0 month**	**At 3rd month**	
	Mean ±SD	Mean ±SD	**P value**	Mean ±SD	Mean ±SD	**P value**
FBS* (mmol/l)[a]	6.9 ±0.6	6.9 ±0.69	0.35	6.8 ±0.6	6.7 ±0.69	0.24
PPBS(mmol/l)[a]**	8.3 ±0.6	8.3 ±0.7	0.54	8.1 ± 0.7	8.0 ±0.69	0.5
HbA1C^(%)[a]	6.9 ±0.6	7.0 ±0.6	0.13	7.0 ±0.6	6.8 ±0.6	0.6
Creatinine(mg/dl)[b]	2 ±0.7	2.2 ±0.6	0.97	2.4 ±0.9	2.4 ±0.9	0.06
eGFR*(ml/min)b**	33.8 ±18.5	32.4 ±12.9	0.34	31.4 ±19.8	33.5 ±21.6	0.08

FBS*: fasting blood sugar **2HABF**:** 2 hours after breakfast
HbA1C^: glycated hemoglobin **eGFR***:** estimated glomerular filtration rate

[a] Paired Sample T test [b] Related Samples Wilcoxon Signed Rank Test

Table IV shows no significant change was noted in FBS, 2HABF, HbA1c, creatinine and eGFR values of both group I and II, when month 0 (basal) values were compared with 3rd month values after giving intervention.

Table V: Comparison between changes of 24 hours proteinuria of both group I and group II in basal, month 1and month 3.

24 hours **of proteinuria (gm/day)**	**group I (mean ± SD)**	**group II (mean ± SD)**	**p value**
Basal	2.2 ± 1.3	2.7 ± 1.42	0.20
Month 1	2.0 ± 1.2	2 .5 ± 1.3	0.19
Month 3	1.95 ± 1.2	1.25± 0.78	0.01

Mann-whitney u test was used

Table V shows mean basal levels of proteinuria was 2.2 ± 1.3 g/day (range 0.63 – 5.0 g/day) for Group I and 2.7 ± 1.42 g/day (range 0.51–5.0g/day) for Group II. It reduced to 2.0 ± 1.2g/day for Group I and 2.5± 1.3 for Group II, at the end of 1 month. At the end of 3 months, a significant decline of proteinuria was observed in both the groups. In Group I it had a mean of 1.95 ± 1.2g/day, whereas it was 1.25± 0.78g/day in Group II. A statistically significant difference existed between the control and study groups ($p < 0.05$), at 3 months.

Table VI. Comparison between mean change in levels of proteinuria (g/day) of both group I and group II.

	Group I (mean ± SD)	**group II (mean ± SD)**	**p- value**
Baseline vs. 1 month	0.17 ± 0.32	0.22 ± 0.14	>0.05
Baseline vs. 3 months	0.46 ± 0.32	1.48 ± 0.9	<0.05

The mean change in the level of proteinuria was 1.48 g/day in the intervention group (Group II) after 3 months of doxycycline therapy, whereas it was 0.46 g/day in the control group (Group I), indicating the beneficial effect of doxycycline in decreasing proteinuria.

After measurement of different variables in both control and intervention group at month 0 both groups were followed up at month 1 and month 3. The control group was kept in their previous medications and the intervention group was given Doxycycline for 3 months.

DISCUSSION

Diabetes and its devastating complications greatly reduce life expectancy and target nearly every organ system in the body. Despite advances in clinical care, the incidence of type 2 diabetes-related cases of ESRD show an increasing trend over the years. Current treatment modalities relies on the nephroprotective and antiproteinuric effects of renin– angiotensin system (RAS) blockade in addition to optimized metabolic and blood pressure control and low salt intake. However, newer treatment options are continuously on research. Doxycycline is a promising drug used for another indication. But based on its pharmacodynamics and pharmacokinetincs it was hypothesized that it may have effect on proteinuria. Therefore, a prospective interventional study was designed to see the effects of doxycycline on proteinuria in diabetic patients with diabetic nephropathy.

Mean age of control group and intervention group were 55.60 ±10 and 54.7 ± 9.5 SD respectively. Though there is no age of development of DN but it was in a study in a study in Indian families in which two successive generations had type-2 diabetes, the likelihood of the offspring developing overt nephropathy was 14% if no parent had proteinuria, 23% if one parent had proteinuria, and 46% if both parents had proteinuria.[12] Similar findings was found Rouhi H et al.,(2013).[13]

Certain base line physical characteristics (SBP, DBP) were collected before intervention. Mean systolic blood pressure of control and intervention group were 131 ± 6.6 and 131± 7.7 respectively; mean diastolic blood pressure were 78± 4.7 and 79± 7.2 respectively. These parameters taken at the end of first month and at the end of third month but there was no significant difference between control and intervention groups ($p > 0.05$). This finding is consistent with similar study by Hari krishan et al., (2010).[14]

Moreover, the effect ofstudy participants were also assessed serum creatinine and e-GFR between control group (I) and intervention group (II) before starting intervention (Doxycycline). There is no significant difference were noted in distribution of serum creatinine ($p=0.14$), e-GFR across groups (p value =0.54). Observation evidenced that there is no significant change was noted in Creatinine and e-GFR values of both group I and II, when month 0 values were compared with month 3 values after giving intervention. Those findings are supported by the study Hari Krishan and Deepak Jain (2010).[14] From this it was assumed that doxycycline has no effect (beneficial/deleterious) on these renal parameters.

The study was focused on to see the effect of Doxycycline on proteinuria. Mean pre-intervention 24 hours proteinuria in 2.2 ± 1.3g/day (range 0.63 – 5.0 g/day) for Group I and 2.7 ± 1.42g/day (range 0.51–5.0g/day) for Group II. Difference in distribution of 24 hours proteinuria between two groups (pre intervention) was not significant (p value 0.2). But following intervention of Doxycycline (oral 100 mg once daily for 3 month) and observation of this two group (intervention and control) at month zero and month 3 showed, a

significant change in 24 hours proteinuria at month 3 in group II (intervention group) (p value = 0.01). The findings is similar to the study done by Hari Krishan et al., (2010).[14] and showed significant reduction of proteinuria in intervention group than control group ($p < 0.05$). similar finding was also supported by Naini, et al.[11]

The delayed response seen after 3 months and not immediately after 1 month may be due to altered expression of MMPs and degradation of ECM proteins in the presence of the drug.[14]

The antiproteinuric effect of doxycycline was achieved with a good compliance and no apparent serious adverse effect.

CONCLUSION

In this study we can conclude that Doxycycline treatment in diabetic patients is capable of preventing progression of DN, instead of simply influencing one of its surrogate end points, albuminuria. Further long-term multicentric trials are required to determine the benefits of doxycycline in patients of DN. Doxycycline has shown to reduction of proteinuria patients, on traditional antiproteinuric drug in diabetic nephropathy.

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