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ASSESSMENT OF ERYTHROPOIETIN STATUS IN EARLY DIABETIC NEPHROPATHY AND ITS CORRELATION WITH MICROALBUMINURIA

Biochemistry

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ABSTRACT

Objectives: To investigate serum Erythropoietin levels in patients with early diabetic nephropathy (<5 years) and analyze the relationship between Erythropoietin and Microalbuminuria.

Methods: Case population comprised of Type 2 diabetic patients in the age group 18-60 years with diabetes persisting for less than 5 years. Diagnostic criteria for case subject with diabetics was done as per ADA 2016 guidelines. A control group of healthy subjects was used for comparison.

Results: Our study shows that Erythropoietin level is significantly decreased in cases in comparison to controls (p value <0.05). A negative correlation exists between Erythropoietin level and ACR value in cases and also a negative correlation exist between ACR and hemoglobin level in cases.

Conclusion: Early Diabetic nephropathy is associated with decreased Erythropoietin level in spite of normal iron storage that warrant frequent monitoring among patients with diabetic kidney disease.

KEYWORDS

Erythropoietin, diabetic nephropathy, Microalbuminuria.

INTRODUCTION

Diabetes is fast gaining status of potential epidemic in India with more than 62 million diabetic individual currently diagnosed with diabetes [1]. Type 2 diabetes mellitus is one of major public health challenge on 21st century with approximately 85-95% of all diagnosed cases of diabetes [1,2]. Diabetes is the leading cause of chronic kidney disease and is associated with excessive cardiovascular morbidity and mortality [1,2]. Anemia is common among those with diabetes and CKD and greatly contributes to patient outcomes [3,4]. Observational studies indicate that low Haemoglobin levels in such patients may increase risk for progression of kidney disease and cardiovascular morbidity and mortality [5]. Diabetes is the most common cause of end stage renal disease [6] and renal anemia. Damaged renal interstitium, systemic inflammation and autonomic neuropathy all contribute to anemia in diabetic nephropathy with renal dysfunction before changes in glomerular filtration rate.

Erythropoietin [EPO]produced mainly by peritubular fibroblast of renal cortex in adult life, whose function is to stimulate and differentiate erythroid progenitor cell of normoblast to increase red cell mass in response to tissue hypoxia due to anemia, haemorrhage, high altitude [6,7]. In diabetic nephropathy, tubulointerstitial hypoxia occurs followed by loss of tubular and peritubular cell reducing the production of 1,25dihydroxy vitamin D3 and erythropoietin[8]. Dysfunction of receptor occurs by diabetic states reducing the trophic effect of hormone. So in presence of normal iron status kidney produce erythropoietin. But in diabetic patients, compromised kidney cannot produce functional erythropoietin manifesting anaemia clinically [9,10]. Anaemic diabetic nephropathy patient show more proteinuria than nonanaemic diabetic nephropathy patient [11, 12, 13]. So it can be said in diabetic patient Erythropoietin level decreases causing anemia with microalbuminuria. But there is less published data of Erythropoietin deficiency and microalbuminuria in early diabetic nephropathy. So our present study is to focus on erythropoietin and microalbuminuria in type 2 diabetes mellitus for less than 5 years i.e. early diabetic nephropathy and to find out a correlation between Erythropoietin and microalbuminuria.

MATERIALS AND METHODS

The study was a hospital-based, case–control study conducted at a tertiary care center in West Bengal, India. The study was approved by the Institutional Ethical Committee of Medical College & Hospital, Kolkata (Memo No: MC/Kol/IEC/Non-Spon/639/11-2017 dated 11.11.2017). Before enrollment of the study participants, written informed consent was obtained from all the participants. The duration of the present study was 12 months and cases comprised of Type 2 diabetic patients in the age group 18-60 years with diabetes persisting for less than 5 years attending the outpatient department. Diagnostic criteria for cases were based on American Diabetes Association criteria 2016. Patients suffering from Type 1 DM, patients with macroalbuminuria and patients suffering with known kidney disease were excluded from the study. Control group comprised of nondiabetic age and sex matched healthy subjects. 10 ml of venous blood sample was collected aseptically from all the cases and controls after 8 hours of fasting. Urine samples of respective cases and controls are collected in sterile urine container for estimation of Microalbumin Creatinine ratio. Biochemical parameters were assayed using fully automated biochemistry analyzer (SCALVO KONELAB 600i PRIME) and Siemens Advia Centaur XP. Routine hematological testing, including complete blood count, was carried out on Sysmex XN instrumentation (XT4000i) followed by slide review by pathologists. The quality of results was validated with internal quality control (IQC) procedures and participation to an External Quality Assessment Scheme (EQAS). The study was carried out in accordance with the Declaration of Helsinki and with the term of the local legislation. Statistical analysis was done by SPSS software version 20.0 and Microsoft Excel 2013. Student's t test was performed and p- value less than 0.05 was considered to be statistically significant. Correlation between variables was determined using linear regression analysis.

RESULTS:

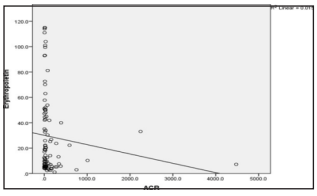
No significant difference was found between the ages of cases and controls (p value 0.15) by independent t-test. No significant difference in sex distribution between case and control has been observed by applying chi-square test.

Table 1: Biochemical parameters of two Groups.

	Test (N= 52)		Control(N= 48)		
	Mean	**SEM**	**Mean**	**SEM**	**p value**
Erythropoietin	15.289	3.649	45.892	9.36	0.001
Haemoglobin	11.21	1.8316	14.04	1.714	0.022
ACR	271.675	89.96	16.074	8.2099	0.018
Iron	92.48	4.415	104.83	13.209	NS
TIBC	315.52	53.465	335.38	43.108	NS
Ferritin	89.750	9.1303	108.626	11.7985	NS

Correlation between Erythropoietin and ACR in Diabetic Nephropathy patient

DISCUSSION



In the present study, it has been found that mean value of ACR for case

was 271.676 mg/gm of creatinine while mean value of ACR for control was 16.074. So mean ACR was significantly (p=0.018) higher in case than in control. The study done by Dhruv.K.Singh et al [8] support outcome of this present study. In their study, 50% of patient with haemoglobin <11 g/dl and 43% of patient with WHO defined anaemia had insufficient iron stores for erythropoiesis (Transferrin saturation<20%). This was marked once renal function fall below 60ml $min^{-1}/1.73m^{-2}$ where there is increase in prevalence of low iron stores compared with general population. They proposed diabetes with Microalbuminuric patient were >2 times and macroalbuminric patient >10 times anaemic than normoalbuminuric patient with renal function (GFR > 80ml/min). Damage to renal interstitium, systemic inflammation and autonomic neuropathy, all contribute to anaemia in diabetic nephropathy. However, patient with diabetes are more vulnerable to the effect of anemia as many of them have significant cardiovascular disease and hypoxia induced renal damage[14]. In this study, mean value of hemoglobin of case was 11.21 and mean value of control was 14.040. p value was 0.022 which was statistically significant . This study was supported by the study done by T.Babazona et al which postulated that decreased hemoglobin concentration was a significant predictor of decline in glomerular filtration rate even in patient without clinical albuminuria. In our study, mean value of Erythropoietin for case was 15.289 and that of control was 45.892. P value was 0.001 which was statistically significant. Deborah R et al had similar finding stating anemia with erythropoietin deficiency occur in early diabetic nephropathy but not in non-diabetic individuals.[16] Thus anemia in diabetic nephropathy patient was associated with erythropoietin deficiency. Erythropoietin deficiency, of the patient with diabetes result from damage to the Erythropoietin producing fibroblast of renal cortex as diabetic nephropathy may involve not only glomerulus but also the renal interstitial area [17]. Our study showed a negative correlation between ACR and erythropoietin in type 2 diabetic individuals. Pearson correlation coefficient r is -0.233 and p value is .024. So correlation is statistically significant. So it can be concluded that as ACR value (microalbuminuria in the range 30-300mg/gm of creatinine) is increasing and erythropoietin value is simultaneously decreasing by the failing kidney. Here none of the patients are with advanced renal disease as almost all with urea level in the range 20-40mg/dl and creatinine level in the range 0.9-1.6 mg/dl (Male) and 0.6-1.2mg/dl (Female). In this study, a negative correlation between ACR and Hemoglobin of diabetic patients was observed. Pearson correlation coefficient r is –0.245and p value is .017. So the correlation is statistically significant as value is <0.05. Thomas MC et al supported this study. [9]

This study has certain limitations. Since the number of patients in the study group was not large, one should be cautious to extrapolate the present findings to any other population. Our present study was conducted in a tertiary care hospital. In our country, a huge section of the population visit district, subdivisional, and lower-tier hospitals for treatment. For this reason, our study results might not reflect the true picture of the entire population. Hence, a multicentric study on a larger population would be required to reveal a more robust statistics. The current study is limited by being cross-sectional study design which only provides the basis for associations rather than causality. Adjustment of confounding factors (due to ethnicity, religion, dietary habit, physical activity etc.) was not performed. Analysis based on treatment history (whether newly diagnosed or on medication) for cases was not considered.

CONCLUSION

Our study suggests in early diabetic nephropathy, erythropoietin deficiency occurs inspite of normal iron status. A negative correlation exist between ACR value and Erythropoietin level. This warrants proper monitoring of patients with microalbuminuria, especially with their increased risk of anemia with nephropathy progression.

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