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Study on Importance of Anaemia as a Risk Factor for Diabetic Retinopathy in Type 2 Diabetes Mellitus

Running title: Anaemia as Risk Factor for DR in Type 2 Diabetics

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ABSTRACT AND KEYWORDS

BACKGROUND

Diabetes mellitus (DM) is a growing medical issue all over the world with Diabetic retinopathy (DR) being the leading cause of acquired yet potentially avoidable blindness. Anaemia can be an individual risk factor in the progression of cardiovascular disease and chronic renal disease along with DR.

AIM

The aim of our study is to prove that anaemia is a risk factor for DR in patients with type 2 diabetes.

MATERIALS AND METHODS

This Hospital based cohort study includes 240 patients of both the genders (130 males and 110 females) with type 2 DM having DR. Blood investigations including haemoglobin levels by colorimetric method, glycosylated haemoglobin (HbA1c) blood urea nitrogen, serum creatinine were also assessed. SPSS version17 was used for statistical analysis.

RESULTS

The mean age of enrolled patients was 56.68±10 years. Of the 240 patients that were included in the study, 92 (38.3%) had diabetes of <5 years, 124 (51.7%) had diabetes of 5-10 years and 24 (10%) had diabetes of >10 years. Of the 480 eyes of 240 patients, 188 (39.1%) had mild NPDR (Non Proliferative Diabetic Retinopathy), 140 (29.2%) moderate NPDR, 140 (29.2%) severe NPDR and 12 (2.5%) had PDR (Proliferative Diabetic Retinopathy). Out of 130males, 21 (16.2%) had haemoglobin level <13g/dl. Out of 110 females, 76 (69%) had haemoglobin level <12g/dl.

CONCLUSION

Frequent screening for DR in all type 2 DM patients is important if patients have longer duration of diabetes, high blood glucose levels, irregular glycaemic control, renal disorders or anaemia due to any cause.

1.INTRODUCTION

Diabetes mellitus (DM) is a growing medical issue and has become a public health challenge throughout the globe. The prevalence of diabetes is rising rapidly all over the globe at an alarming rate.[1] India leads the world with largest number of diabetic patients being termed the "diabetes capital of the world". Diabetes is a metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Type 2 DM, also referred to as non–insulin dependent DM, encompasses individuals who have insulin resistance and usually have relative, rather than absolute insulin deficiency accompanied by failure to produce sufficient insulin. Prolonged hyperglycaemic status due to DM can lead to microvascular and macrovascular complications. The microvascular complications include retinopathy, nephropathy and neuropathy, while coronary artery disease, cerebrovascular disease and peripheral artery disease are grouped as macrovascular complications.

Diabetic Retinopathy (DR) is one of the leading causes of acquired, yet potentially avoidable blindness. This is a microangiopathy that affects the retinal precapillary arterioles, capillaries and venules. Its progression depends on defective carbohydrate metabolism, duration of disease, control of hyperglycaemic status and oxidative stress.[2] Anaemia can be an individual risk factor in the progression of DR. This is due to hypoxia of the retinal tissue that adds to the progression and severity of retinopathy in diabetic patients.[3]

The US based ETDRS(Early Treatment Diabetic Retinopathy Study) showed that early diagnosis and treatment of anaemia could decrease the rate of progression of retinopathy in type 2 DM patients.[4] More frequent screening of diabetic patients for progression of DR is important, if they have anaemia or renal disorder in order to prevent rapid progression of retinopathy and vision threatening complications. Hence, the aim of our study is to prove that anaemia is a risk factor for DR with low haemoglobin level being a predictor of diabetic nephropathy.

2. MATERIALS AND METHODS

This hospital – based cohort study was conducted over a period of 2 years on 240 patients with Type 2 DM who attended outpatient clinic in the department of ophthalmology in a tertiary care centre in South India.

Ethical Approval:

This study was approved by the Institutional Ethics Committee (Ref No: CSP-MED/14/SEP/18/145) and was conducted according to the tenets of declaration of Helsinki.

Inclusion criteria: Patients with a confirmed diagnosis of Type 2 DM established or recently diagnosed with clinical evidence of DR changes.

Exclusion criteria: Patients with pre - existing renal diseases or diabetic nephropathy, patients with type 1 DM, hypertension, dyslipidaemia, pregnancy, chronic liver disease, malignancy, blood disorders or significant media opacities precluding fundus examination.

All patients were well informed about the study and an informed written consent was obtained. Background data included age, sex, occupation, type of diabetes, duration of diabetes, blood pressure, personal history, lifestyle and treatment history. Their ophthalmic clinical data included BCVA, slit-lamp evaluation, intraocular pressure and fundus examination. Fasting and postprandial blood sugars were measured using glucose oxidase method. Haemoglobin levels by colorimetric method, blood urea nitrogen, serum creatinine and glycosylated haemoglobin was recorded using high performance liquid chromatography. Proliferative retinopathy was confirmed with fundus fluorescein angiography. Patients with fasting blood sugar >126mg/dl, postprandial blood sugar >140mg/dl, HbA1c >5.7% were considered as diabetic. Haemoglobin levels <13g/dl in males and <12g/dl in females were considered as anaemic.

Statistical Analysis:

Data was analyzed using Statistical Package for Social Science (SPSS) version 17 for Microsoft windows. The normally distributed data were expressed as Mean and Standard Deviation. Descriptive statistics were presented as numbers and percentages. One way analysis of variance with a post hoc Tukey Honestly Significant Difference (HSD) was used for normally distributed continuous data. Chi - squared test was used for comparison between two attributes. Two sided p value of < 0. 05 were considered statistically significant.

3.RESULTS

This study involved 480 eyes of 240 patients, 130 males (54.2%) and 110 females (45.8%). The mean age of enrolled patients was 56.68±10.1 years. Visual acuity on presentation of 240 patients is shown in [Table 1]. The grading of DR was done according to the ETDRS classification. Of the 480 eyes of 240 patients with DR, 188 (39.1%) had mild NPDR, 140 (29.2%) had moderate NPDR, 140 (29.2%) had severe NPDR and 12 (2.5%) had PDR. Of the 240 patients, 92 (38.3%) had diabetes of <5 years, 124 (51.7%) had 5-10 years and 24 (10%) >10 years. The mean duration of diabetes for mild NPDR was 2.9±1years, moderate NPDR 6.5±1.8 years, severe NPDR 8.5±3.3 years and PDR 15.8±1.4 years.

Among 240 patients, 97 (40.4%) had low haemoglobin. Out of 130males, 21 (16.2%) had haemoglobin level <13g/dl, and out of 110 females, 76 (69%) had haemoglobin level <12g/dl. The mean values of haemoglobin in mild NDPR, moderate NDPR, severe NDPR and PDR were 14.8±1.5, 13.8±2.5, 9.6±1.3 and 10.08±0.9 respectively. The mean HbA1c levels for mild NPDR was 6.19±0.4, moderate NPDR was 7.5±0.6, severe NPDR was 8.8±0.7 and PDR was 9.9±0.3. Out of 240 patients 26 (10.8%) were into business, 124 (51.7%) were employed and 90 (37.5%) were unemployed. History of smoking was present in 57 (22.8%) with p value <0 .001, which indicates a positive relation between smoking and DR. History of alcohol intake in 75 (31.2%) with p value <0.001 points to a significant relationship between alcohol intake and DR. One hundred and thirty nine patients (57.9%) had sedentary lifestyle which suggests that more sedentary behaviour was associated in this section.

4.DISCUSSION

Diabetic Retinopathy is a highly specific vascular complication related to diabetes. DR is characterized by gradually progressive changes in the retinal microvasculature, which leads to retinal hypoperfusion, increased vascular permeability and proliferation of abnormal retinal vessels. Chronic hyperglycaemia is the main initiating factor for all types of diabetic micro-vascular changes.[5] It causes abnormalities in RBC, oxidative stress, renal sympathetic denervation causing hypoxia in renal interstitium and decreases the production of erythropoietin by peritubular fibroblast which leads to progression of anaemia. Anaemia is more prevalent in persons with diabetes than in persons without diabetes.[6] The prevalence of anaemia in diabetic patients is estimated to be 14 - 48%.[7] It is a common accompaniment to diabetes potentially contributing to the pathogenesis of retinopathy. Anaemia is known to develop earlier in diabetic individuals and is more severe in diabetic patients than in patients with renal impairment from other causes.[8] Anaemia can lead to falsely low HbA1c levels, which may result in under treatment of hyperglycaemia, which in turn will contribute to the progression of retinopathy. Early detection and treatment of anaemia can decrease the number of micro aneurysms and resolution of hard exudates.[9] The aim of this study was to assess the correlation between anaemia and DR in type 2 DM patients attending the Ophthalmology outpatient clinic. Our study showed a positive correlation (p - value <0 .001) between the duration of diabetes and the severity of retinopathy. Comparison between duration of diabetes and severity of retinopathy is given in [Graph 1]. The study by Dandona et al has also shown that duration of diabetes is

the best predictor for retinopathy.[10] Anaemia was found to be risk-factor of DR in our study. Patients with anaemia were more likely to develop DR than patients without anaemia, may be due to anaemia adds to retinal hypoxia. Hypoxia may cause changes in angiogenesis, capillary permeability, vasomotor response, and cell survival.[11] In our study 21 (16.2%) out of 130 male were anaemic and 76 (69%) out of 110 females were anaemic. Comparison between haemoglobin level and severity of retinopathy is given in [Graph 2]. This depicts a significant relationship (p - value <0 .001 using chi - square test) between anaemia and DR. David et al in ETDRS evaluated the effect of moderate levels of anaemia by haematocrit measurements.[4] They reported that in their lowest haematocrit group (defined as male <40%, female < 34%), anaemia was observed to be an independent risk factor with odds of 1.52 times for the development of high risk proliferative retinopathy and of severe visual loss over a 5 year follow-up. Quing Quio et al reported odds of 5.0 for severe retinopathy with presence of anaemia.[12] Shorb et al reported that diabetic patients with severe iron deficiency anaemia rapidly progressed to severe proliferative retinopathy. In patients who had both anaemia and DM, Friedman and associates reported that treatment with erythropoietin was correlated with substantial resolution of macular hard exudates. The improved haemoglobin concentration with therapy of anaemia improves tissue oxygenation and may result in reduced VEGF (Vascular Endothelial Growth Factor) production, which improves the hyper permeability and reduces the stimulus for neovascularization. These observations suggest that anaemia evaluation should be considered in the routine screening of diabetic patients and should be identified and treated early to minimize the risk of microvascular complications. The mean HbA1c levels for mild NPDR were 6.1±0.4, moderate NPDR was 7.5±0.6, severe NPDR was 8.8±0.7 and PDR was 9.9±0.3. This provides fair evidence that increased HBA1C levels influence the severity of retinopathy.

Our study showed some other correlations like higher the age, higher the retinopathy stage with the mean age of the patients being 56.6±10. The study by R Khandekar et al, showed that the retinopathy rate was higher in age group 50 - 59 years. The female to male ratio in this study was 1:1.2. A study conducted by Mohan Rema et al and Khandekar et al also showed a preponderance of retinopathy in men. According to Zuphen study, cigarette smoking plays an important role in the development of DR. Our study also showed a positive relation between smoking and DR with a p-value of <0.001. Young et al reported heavy alcohol consumption to be a risk factor for the development of DR which was in accordance with our study with a p value of <0.001. In this study, 139 (57. 9%) had sedentary lifestyle which provides some suggestive evidence that more sedentary behaviour was associated with higher odds of having DR.

Limitation of this study included a small sample size and lack of follow-up. The values were recorded and co-related at one point of time. Frequent follow-up with the impact on DR with correction of anaemia in a large group study could have given a more reliable and clear picture.

5.CONCLUSION

The incidence of DR was more in males and more in 40 - 60 years of age. Our study shows that anaemia is an important risk factor for DR and Haemoglobin being the major predictor for reduced erythropoietin levels could be an early sign of diabetic nephropathy. Healthy life style modifications complement in decreasing the risk for DR. Hence more frequent screening for DR along with haemoglobin levels and treating underlying anaemia could play a major role in preventing the progression of the disease and also insists the importance of the holistic care for the wellbeing of the patient.

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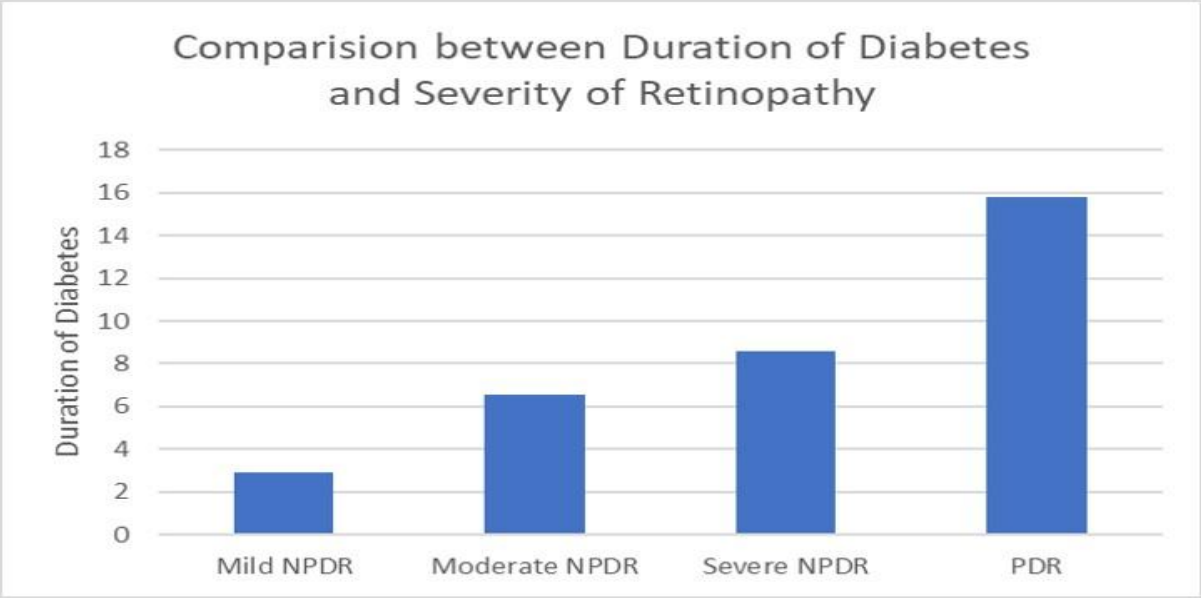
8.FIGURES AND TABLES

Visual Acuity on presentation	No. of Eyes	Percentage
6 / 9	70	14.6
6/12	54	11.3
6/18	77	16
6/24	50	10.4
6/36	58	12.1
6/60	47	9.8
3/60	57	11.9
2/60	45	9.4
1/60	12	2.5
CFCF	6	1.3

HMCF	4	0.8
Total	480	100

Table 1: Visual Acuity in Percentage

Graph 1



Graph 2