ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 4, Issue – 6, November – December - 2021, Page No. : 100 – 106

Association of Serum Magnesium and HbA1c Levels with Diabetic Retinopathy in Type II Diabetes Mellitus Patients- An Observational Study at Rajarajeswari Medical College and Hospital

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How to citation this article: T M Nithisha, R Neha, "Association of Serum Magnesium and HbA1c Levels with Diabetic Retinopathy in Type II Diabetes Mellitus Patients- An Observational Study at Rajarajeswari Medical College and Hospital", IJMACR- November – December - 2021, Vol – 4, Issue - 6, P. No. 100 – 106.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Type II Diabetes Mellitus is a multi-factorial disease characterized by hyperglycemia. Hypomagnesemia, often underdiagnosed electrolyte abnormality is known to be associated with diabetes control and its complications. Therefore, an attempt is made to evaluate the relationship between Serum Magnesium and HbA1C (Glycosylated Hemoglobin) levels with Diabetic Retinopathy.

Methods: In this observational hospital based study, a total of 150 Type II Diabetes Mellitus patients were evaluated based on history, ocular examination and blood investigations. Data was collected and analyzed.

Results: Out of 150 patients, 100 (66.67%) were males and 50 (33.33%) were females. The prevalence of Diabetic Retinopathy was 84%. A statistically significant correlation was found between increasing serum HbA1C level and hypomagnesemia with severity of Diabetic Retinopathy.

Conclusion: Risk factors such as duration of Diabetes Mellitus, glycemic control and hypomagnesemia should be considered for regular check-up and early detection of Diabetic Retinopathy.

Keywords: Diabetic Retinopathy, HbA1C, Hypomagnesemia, Type 2 Diabetes Mellitus

Introduction

Diabetes Mellitus (DM) is a multi-factorial metabolic disease characterized by hyperglycemia resulting from defective insulin secretion or insulin resistance in peripheral tissues. [1] Globally, the number of people with diabetes is estimated to be 422 million in 2019 and projected to rise to 629 million by 2045 with a major rise in India. [2] World Health Organization (WHO) has labeled India as "The Diabetic Capital of the World" and every fifth diabetic in the world is an Indian. [3] The

multisystem effects of diabetes such as retinopathy, nephropathy, neuropathy and cardiovascular diseases have an impinging effect on the working age individuals in our country. [3] Diabetic Retinopathy (DR) is a micro-angiopathy that exhibits feature of both micro-vascular occlusion and leakage with characteristic picture in the fundus. DR is among the most common ophthalmic complication of DM, it is also the leading cause of legal blindness. [4] DR is strongly associated with longer duration of diabetes and poor glycemic control. [5]

HaemoglobinA1c (HbA1c) testing is an important test for the diagnosis and monitoring of diabetes mellitus [6], it is a measure of glycation of β-N-(1-deoxy)-fructosyl hemoglobin contained within the red blood cell. [7] HbA1C has been known to be a marker to assess the long term control of diabetes mellitus. Expert opinion recommends HbA1c testing at least two times a year in patients who have stable glycemic control and four times yearly in poorly controlled individuals. [7]

Magnesium is the fourth most common cation in the body, it was previously underappreciated, but now established as a central electrolyte in a large number of cellular metabolic reactions. [8] Low magnesium status has been repeatedly demonstrated in patients with diabetes. [9] Magnesium deficiency appears to have a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes. [10]

Hypo-magnesemia has been definitely shown to be associated with increased risk of Diabetes Mellitus, but its association with retinopathy has been inconclusive and hence this current study has been undertaken to evaluate the association of serum levels of magnesium with retinopathy in type 2 diabetes and correlation with long term control of diabetes mellitus.

Methodology

This study was conducted in the Department at Rajarajeswari Medical College & Hospital, Kambipura, Bengaluru, from December 2019- December 2020.

Inclusion Criteria: All patients diagnosed with Type II Diabetes Mellitus of either sex were considered for the study.

Exclusion Criteria: Patients with hazy media, pre-existing non diabetic maculopathy, myopic degenerations and other retinal degenerations, in whom dilatation of pupils is contraindicated, taking anti-platelet medications, taking diuretics, taking magnesium supplementation, taking magnesium containing antacids, malabsorption syndrome, chronic diarrhea, renal failure, liver diseases, tuberculosis and thyrotoxicosis, diabetes mellitus less than five years, type I diabetes mellitus were excluded from the study.

150 cases were enrolled for the study. Ethical committee clearance was obtained from the institutional review board. Those patients with Type II Diabetes without any associated systemic morbidity were taken as cases and studied for DR.

Detailed history of each patient was obtained regarding the age, duration of diabetes, the antidiabetic treatment they were on and any associated illness. The duration of diabetes was reckoned from the onset of significant symptoms. General physical examination was performed following which a complete ophthalmological examination including determination of visual acuity, slit lamp bio microscopy, intraocular pressure and fundus examination was performed. Retinopathy was classified after a fundoscopic examination as Non Proliferative Diabetic Retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR). Fundus fluorescein angiography was

performed only when clinically necessary. All the findings were documented in the proforma.

Based on the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria, patients were graded according to their severity of retinopathy. Fasting blood sample was used to assess HbA1C level, serum electrolytes including serum magnesium and blood sugar level. In case of patients with asymmetric fundus findings, the eye with a more severe grade of diabetic retinopathy was taken into consideration. We considered values normal when HbA1C levels were less than 7% and serum magnesium level in the range between 1.8 to 2.5 mg/dl.

Table 1: Mean duration of Diabetes in different severity of DR

Severity of DR	Mean Duration of DR (in years)	StandardDeviation (S.D) (in years)	95% Confidence Interval for Mean (in years)	
			Lower Bound	Upper Bound
No DR	8.04	2.98	6.85	9.23
Mild NPDR	11.11	5.55	7.48	14.74
Moderate NPDR	10.72	5.00	9.15	12.29
Severe NPDR	13.35	5.71	11.16	15.54
Very Severe NPDR	12.66	6.30	8.30	17.02
PDR	13.48	4.85	12.05	14.91

The collected data was analyzed using MS-Excel and Statistical Package for the Social Sciences (SPSS) version 20.0. ANOVA F test and Fischer's exact test were used for the analysis of the data obtained. Results were evaluated in 95% confidence interval and p value of <0.05 was considered as significant.

Results and Discussion

DR is an emerging public health problem with both medical and economic considerations involved. Accurate data concerning the type and severity of DR and associated risk factors are of importance in planning a well-coordinated approach to the public health problem posed by this complication of diabetes. Identifying the patient who may be at high risk of severe retinopathy is important in advising ophthalmic care. Such data is also helpful in planning future studies such as controlled clinical trials of treatment of diabetes and of diabetic retinopathy.

In a total of 150 diabetic patients, 100 (66.67%) were males and 50 (33.33%) were females, with a male to female ratio of 2:1. The prevalence of Diabetic Retinopathy in the study population was 84%, among them 86 (68.25%) were males.

The study population was categorized based on duration of diabetes and severity of DR (Table 1). No DR, mild and moderate NPDR were seen in patients with diabetes duration of less than 12 years, whereas severe, very severe NPDR and PDR were seen in patients with diabetes duration of more than 12 yrs. It is evident from these findings that there was a statistically significant worsening of retinopathy and progress of the severity of retinopathy with increasing duration of diabetes in these individuals ($p<0.05$).

Table 2: Relationship between HbA1c level and grade of DR

Severity Of DR	No. of cases	Mean HbA1c	S.D	95% Confidence Interval For Mean	
				Lower Bound	Upper Bound
No DR	24	7.9108	1.363	7.3656	8.456
Mild NPDR	9	8.1667	1.428	7.2337	9.0997
Mod. NPDR	39	7.9346	1.229	7.679	8.1902
Severe NPDR	26	8.7173	1.464	8.1547	9.2799
Very Severe NPDR	8	8.4675	1.489	7.4362	9.4988
PDR	44	8.4548	1.201	8.0998	8.8098

In the CURES Eye study [11], 41.8 per cent had DR after 15 years of diabetes and severity of DR proportionally increased with longer duration of diabetes. In addition, it has been demonstrated that for every five-year increase in duration of diabetes, the risk for DR increased by 1.89 times. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the widest and most prolonged population based ophthalmologic survey, reported that higher prevalence of DR was associated with longer duration of diabetes. [12]

In our study we found a cut off range of HbA1C for different grades of diabetic retinopathy above which retinopathy of that grade tended to manifest: for mild NPDR the range of HbA1c was found from 7.23% - 9.10%, moderate NPDR the range was 7.70% - 8.20%, severe NPDR the range was 8.15% - 9.30%, very severe NPDR it was 7.44% - 9.50% and for PDR the range was 8.10% - 8.81%. Such cut-off ranges have not been evaluated by many, only a few studies have defined such cut off values.

Table 3: Relationship between HbA1c levels and prevalence of DR

HBA1c	No DR n (%)	Mild NPDR n (%)	Mod. NPDR n (%)	Severe NPDR n (%)	Very Severe NPDR n (%)	PDR n (%)	Total
≤7.0	8 (33.33)	2 (22.22)	10 (25.64)	5 (19.23)	2 (25)	5 (11.36)	32
>7.0	16 (66.67)	7 (77.78)	29 (74.36)	21 (80.77)	6 (75)	39 (88.64)	118

Table 4: Relationship between Serum Mg level and grade of DR

Severity of DR	No. of cases	Mean Serum Mg	S.D	95% Confidence Interval For Mean	
				Lower Bound	Upper Bound
No DR	24	2.1708	0.27	2.0628	2.2788
Mild NPDR	9	2.2222	0.181	2.1042	2.3402
Moderate NPDR	39	1.9538	0.354	1.8428	2.0648
Severe NPDR	26	1.8577	0.347	1.7247	1.9907
Very Severe NPDR	8	1.75	0.436	1.448	2.053
PDR	44	1.8	0.394	1.683	1.917

The glycemic status of the patient was evaluated using HbA1c level, which showed a rise with the increasing severity of diabetic retinopathy in a statistically significant manner (p=0.049, p<0.05). Relationship between HbA1c level with grade of DR and prevalence of DR is depicted in Table 2 and 3. One of the studies conducted previously by Garg P [13] et al in this regard showed that patients having a good glycemic control had lower prevalence of diabetic retinopathy as compared to those having poor control. Similar results were derived at Manaviat MR et al [14] who stated that Hba1c was higher in the patients with severe grade of DR. In a study conducted on Malaysian population showed that good glycemic control is proven to reduce the progression of DR in T2DM patients [15], and further reduced the risks of retinal photocoagulation or vitrectomy and macular edema [16].

The present study revealed lower levels of serum magnesium in diabetic patients with retinopathy as compared to patients without DR. The range of serum Mg in mild NPDR: 2.10 – 2.34 mg/dl, moderate NPDR: 1.84 – 2.06 mg/dl, severe NPDR: 1.72 – 1.99 mg/dl, very severe NPDR: 1.45 – 2.05 mg/dl and for PDR: 1.68 – 1.91 mg/dl, were observed. These results were statistically significant (p=0.019, p<0.05).

Table 5: Relationship between Serum Mg level and prevalence of DR

Serum Mg	No DR n (%)	Mild NPDR n (%)	Moderate NPDR n (%)	Severe NPDR n (%)	Very Severe NPDR n (%)	PDR n (%)	Total
<1.8	2 (8.33)	0 (0)	8 (20.51)	10 (38.46)	4 (50)	16 (36.36)	40
1.8-2.5	22 (91.67)	9 (100)	31 (79.49)	16 (61.54)	4 (50)	28 (63.64)	110

Relationship between Serum Mg level with grade of DR and prevalence of DR is depicted in Table 4 and 5. These observations are similar to Kundu D et. al [17] and a Durak R. et. al [18], who studied hypomagnesemia as possible risk factor in the development and progression of diabetic retinopathy. Some studies revealed that hyperglycemia contribute to hypomagnesemia by causing depression in the net tubular reabsorption of magnesium [18 & 19]. Hypomagnesemia has been known to be associated with Diabetes Mellitus [20].

Though multifactorial in etiology, it is mainly due to increased renal losses of magnesium that accompany glycosuria.

Our study showed that increased HbA1c level, increased duration of diabetes and decreased serum Mg is a contributing factor in the degree of Diabetic Retinopathy and this correlation can be explained by the common mechanism involved in tissue damage by diabetes mellitus.

Conclusion

There is a significant decrease in serum magnesium and increase in HbA1c level, furthermore, increase in duration of diabetes in different stages of Diabetic Retinopathy is also seen. The assessment of HbA1c and serum magnesium concentration is inexpensive and easy to employ. It may be prudent in clinical practice to periodically monitor serum magnesium and HbA1c levels in diabetic patients in order to halt the progression of Diabetic Retinopathy by increasing dietary intake or oral supplementation and glycemic control. Dietary supplementation of Mg, in addition to its known benefits in diabetic nephropathy, may lessen ocular morbidity, thereby potentially improving quality of life and vision among type 2 diabetes patients.

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