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EVALUATION OF SERUM MAGNESIUM LEVELS AS A RISK FACTOR IN PATIENTS OF DIABETIC RETINOPATHY

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ABSTRACT **Background:** Magnesium acts as a co-factor in numerous enzymatic reactions. Deficiency of magnesium disturbs carbohydrate metabolism, which leads to hyperglycemia The present study was carried out to evaluate serum magnesium levels in diabetic retinopathy and correlate it with severity of disease.

Method: The present study was carried out in 200 subjects aged 30 to 80 years consisting of 50 healthy non-diabetic subjects (Control) and 150 patients with diabetic retinopathy (Cases). Biochemical analysis of serum magnesium, fasting blood glucose and lipid profile was carried out and correlated with the clinical presentation of the cases.

Result: Serum magnesium levels in diabetic retinopathy patients were significantly lower in diabetic retinopathy as compared to controls. The levels of magnesium were significantly lower in progressive retinopathy as compared to non-progressive retinopathy.

Conclusion: Diabetic retinopathy is associated with magnesium deficiency which may benefit from magnesium supplementation.

KEYWORDS : Magnesium; Diabetic Retinopathy; Diabetes Mellitus

INTRODUCTION

Diabetes Mellitus is a complex metabolic disease caused by a variable interaction between hereditary and environmental factors. It is one of the most common metabolic diseases in which either the hormone insulin is lacking or the body's cells are insensitive to insulin effects [1-3]. It is one of the main threats to human health in the 21st century. It is the leading cause of blindness between the age of 20 to 74 years [4]. The chance of losing the sight is about 25 times higher compared to normal individuals. Blindness is primarily the result of progressive diabetic retinopathy [5,6].Diabetic retinopathy is a complication of diabetes mellitus that affects eyes [7]. It is caused by damage to the blood vessels of the light-sensitive tissue, retina because of hyperglycaemia. The estimated prevalence of diabetic retinopathy among individuals with both diagnosed and undiagnosed diabetes mellitus, ranges from 17.6% in a study in India [8] to 33.2% in a large U.S. study [9]. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade of the disease or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia. Proliferative diabetic retinopathy is marked by neovascularization which is formed in response to retinal hypoxemia. These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment.

Low magnesium status in type 2 diabetes mellitus reduces insulin sensitivity and may increase risk of secondary complication [10]. In recent years scientists are of the view that magnesium has an association with the development of Diabetic Retinopathy [11-13]. Magnesium is one of the most common elements found in the earth's crust and is a macro mineral for human beings. It has been observed that decreased levels of magnesium cause decreased activity of kinase enzymes which in turn lead to altered carbohydrate metabolism that leads to hyperglycaemia in diabetes mellitus. De Valk H.W. et al found an association between low magnesium level and progression of retinopathy [14]. Diabetes mellitus, both type I and type II, are said to be the commonest causes of magnesium deficiency, with 25-39% of patients being affected [14].

The present study was done to evaluate serum magnesium as an important risk factor in the development of retinopathy in diabetic patients as compared with normal healthy subjects.

MATERIALS AND METHODS

The study was conducted in the Department of Biochemistry, Patna Medical College, Patna, Bihar, India. The approval of the institutional ethics committee was taken before starting the study. A written and informed consent was taken from all the patients enrolled for the study after explaining them the aims and objectives of the study.

For this study 50 healthy non-diabetic individuals were taken as control (Group 1) and 150 patients of diabetic retinopathy were taken as cases (Group 2). Both control and case group were between 30 to 80 years old inclusive of both males and females. Patients with altered kidney function, creatinine level >1.5 mg/dl, those on any drugs affecting magnesium levels, alcoholic or suffering from chronic diarrhoea or chronic liver disease or HIV infection were excluded from study.

Detailed history was taken from all subjects followed by clinical examination which included Blood pressure estimation, chest and CVS examination. Direct and indirect ophthalmoscopic examination was carried out to find out the pathology of lens, vitreous and retina which included cataract, vitreous haemorrhage, microaneurysm, dot-blot haemorrhage, soft and hard exudates, cotton wool exudates, macular oedema, neovascularisation or retinal haemorrhage.

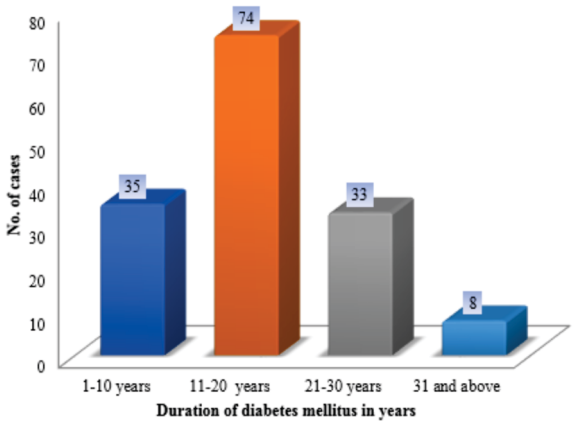
Fasting blood sample was collected for estimation of plasma glucose, lipid profile and serum magnesium. Proper precautions were taken while collecting blood samples to ensure safety of self and to the patient. Standard procedures were used to obtain accurate results at every step.

Serum magnesium was estimated with calmagite dye method. Fasting Blood glucose and lipid profile were estimated by standard methods on automated analyzers.

For data analysis, data was presented as the mean and SD. Statistical analysis were performed by the student 't' test using MS-Excel. A 'p' value <0.05 was considered to be statistically significant.

RESULT

Out of total 150 patients of diabetic retinopathy, number of male patients were 71(47.33%) and number of female patients pathy were 79(52.67%). From the history, the patients developing diabetic retinopathy were divided into four quartiles based on the number of years since diagnosis of diabetes. Maximum patients 49.34% developed retinopathy within 11-20 years of diagnosis of Diabetes (Graph 1).



Graph 1 Graph showing number of diabetic retinopathy cases after the diagnosis of diabetes mellitus in years.

In early patients of Diabetic Retinopathy, the main presentation was non-progressive Diabetic retinopathy, whereas in late cases, most patients presented with progressive retinopathy (Table 1).

Table 1:Showing distribution among the different groups according to the duration of diabetes mellitus in years with the type of diabetic retinopathy

Sl. No.	Groups	Duration of diabetesmellitus in years	Type of diabetic retinopathy	No.of cases	Percentage
1.	Control	NonDiabetic	0	0	0
2.	Patient	1-10	NPDR	34	22.67%
			PDR	1	0.67%
		11-20	NPDR	68	45.33%
			PDR	6	4%
		20-30	NPDR	6	4%
			PDR	27	18%
		31andabove	NPDR	0	0%
			PDR	8	5.33%
		Total	**NPDR**	**108**	**100%**
			PDR	**42**	

NPDR – Non proliferative diabetic retinopathy PDR – Proliferative diabetic retinopathy.

The fasting blood glucose, blood pressure, Serum cholesterol, serum triglycerides and serum LDL of non-diabetic patients were significantly lower than diabetic patients , whereas serum magnesium and serum HDL were significantly higher (Table 2).

Table 2: Difference in clinical and laboratory parameters between the control group and the study group.

Parameter	Control group (n=50)		Diabetic retinopathy group (n=150)		p-value
	Range	Mean ± SD	Range	Mean ± SD	
Systolic BP (mm Hg)	110-136	120.64 ± 7.34	110-174	137.9 ± 18.78	<0.001
Diastolic BP (mm Hg)	70-96	82.28 ± 8.22	70-116	93.04 ± 11.89	<0.001
Fasting Plasma Glucose (mg/dl)	71-106	84.0 ± 7.85	105-182	148.113 ± 17.26	<0.001
Serum Cholesterol (mg/dl)	111-212	167.34 ± 24.62	126-329	220.08 ± 43.12	<0.001
Serum Triglycerides (mg/dl)	54 – 153	99.72 ± 31.10	90-574	250.95 ±86.56	<0.001
Serum HDL (mg/dl)	41-66	49.0 ± 6.33	25-60	40.94 ± 7.63	<0.001
Serum LDL (mg/dl)	57-102	85.8 ± 12.04	72-190	120.9 ± 31.40	<0.001
Serum Magnesium (mg/dl)	1.53-2.42	1.982 ± 0.21	0.71-2.12	1.35 ± 0.316	<0.001

The diabetic retinopathy cases were further divided into two groups based on type of retinopathy-Non-progressive (NPDR) and Progressive Retinopathy (PDR). Serum magnesium levels were significantly lower in patients with progressive DR as compared to NPDR (Table 3).

Table 3:Comparison of serum magnesium levels in Non-progressive and Progressive Diabetic Retinopathy

Group		No. of subjects	Serum magnesium (mg/dl)				'p'
			Range	Mean	SD	SEM	
Control		50	1.53-2.42	1.982	0.211	0.298	
Patient	NPDR	108	1.02-2.12	1.478	0.265	0.025	<0.001
	PDR	42	0.71-1.47	1.018	0.154	0.023	<0.001

SD – Standard Deviation
SEM – Standard Error of Mean
NPDR – Non proliferative diabetic retinopathy
PDR – Proliferative diabetic retinopathy.

DISCUSSION

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It serves as a cofactor for all enzymatic reactions that require ATP and is a key component in various reactions that require kinases [15]. Since Magnesium is involved in insulin secretion, binding and activity at multiple levels, cellular magnesium deficiency can alter membrane bound sodium-potassium-ATPase activity which is involved in the maintenance of gradients of sodium and potassium and in glucose transport [16].

In the present study in Group 2(Diabetic Retinopathy) there were 71 male and 79 female which shows that the prevalence of diabetic retinopathy among females is more. This goes against the study done by Klein R et al [17] and Rema et al [18] where they stated that prevalence among males is more common. This may be due to the fact that males are more conscious about their health than female in this region of India (Bihar).

The duration of diabetes is probably the strongest predictor for the development and progression of retinopathy. Many times, there is a delayed diagnosis of diabetes mellitus due to ignorance of patient or due to other complication of diabetes mellitus because of belief in parallel therapy like homeopathy or ayurvedic medication or inability to sustain expenses of medical therapy. In this study it had been found that after 20 years of diabetes mellitus the percentage of diabetic retinopathy patient is decreased. This may be due to demise of the patient of that duration. This study is in conformity with Diabetes Control and Complications Trial Research Group [19] and Rema et al [18]. Wisconsin Epidemiologic Study of Diabetic Retinopathy [17], the widest and most prolonged population based ophthalmologic survey has also reported that increase in prevalence of diabetic retinopathy was associated with longer duration of diabetes mellitus.

This study also shows that diabetes mellitus is strongly associated with the development and progression of diabetic retinopathy and that the concentration of fasting blood glucose level in patients of diabetic retinopathy is significantly raised. The results of present study are quite similar to those reported by other researchers in recent studies [14-16].

In the present study, patients with Diabetic retinopathy had significantly lower serum magnesium levels as compared to healthy controls. The results of present study is in conformance with results of several researchers published recently [20-24].

In this study, it is further noted that as severity of diabetic retinopathy increases from non- proliferative diabetic retinopathy to proliferative diabetic retinopathy serum magnesium level goes lower. The exact cause is not known but magnesium is necessary for many enzymes that play a role in glucose metabolism and diabetic retinopathy.

Magnesium depletion in diabetes may result from lower dietary intake, increased urinary loss either due to osmotic diuresis or rampant use of loop and thiazides diuretics which promote magnesium wasting [25,26], and impaired absorption of magnesium compared to healthy individuals. Some of the researchers have also postulated that increased urinary losses of magnesium may result from a specific tubular defect in magnesium reabsorption in thick ascending loop of Henle [27].

Magnesium depletion may alter cellular glucose transport, reduce pancreatic insulin secretion, may result in defective post receptor

insulin signaling, or altered receptor interactions which reduces insulin sensitivity. As the mean magnesium level decreases, severity of retinopathy increases [28].

Recently, Dasgupta A., et al from Assam reported higher incidence of retinopathy in the hypomagnesemia group (64% vs 45.8%) [29]. The existence of a close relationship between impaired magnesium balance and retinopathy was established by Fujii et al., who found a marked depletion in plasma and erythrocyte magnesium levels in diabetic patients with advanced retinopathy [22].

Baig et al reported that the lower levels of serum magnesium may have a bearing on the complication and morbidity in patients of diabetes mellitus, and estimation of serum levels of serum magnesium may be helpful to monitor the severity of diabetic retinopathy in diabetic patients [30]. He further suggested that hypomagnesemia may inhibit prostacyclin receptor function which can produce an imbalance between prostacyclin and thromboxane effects resulting in marked atherogenic potential responsible for microvascular complications [31].

Hence, it become important to monitor serum magnesium levels early in Diabetes mellitus so that oral magnesium supplementation may be initiated which may be helpful in reducing the onset and progression of diabetic retinopathy.

CONCLUSION

Low serum magnesium level and raised fasting blood glucose have direct and positive correlation with development and severity of diabetic retinopathy. It can be concluded that low serum magnesium in diabetic patient can act as strong and most promising biomarker for the risk of microvascular complications like retinopathy in diabetic patient.

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